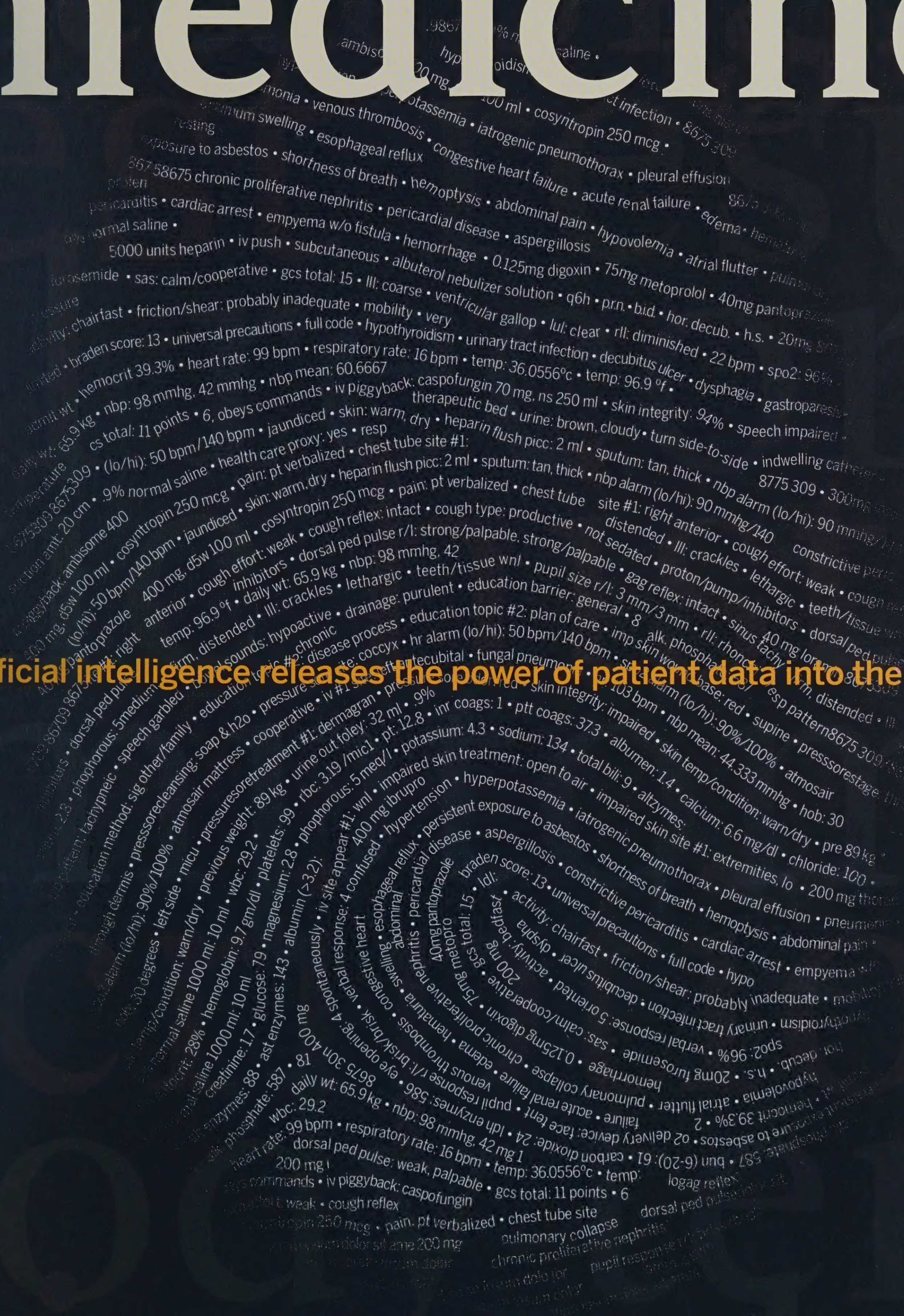
HARVARD medicine

WINTER 2019

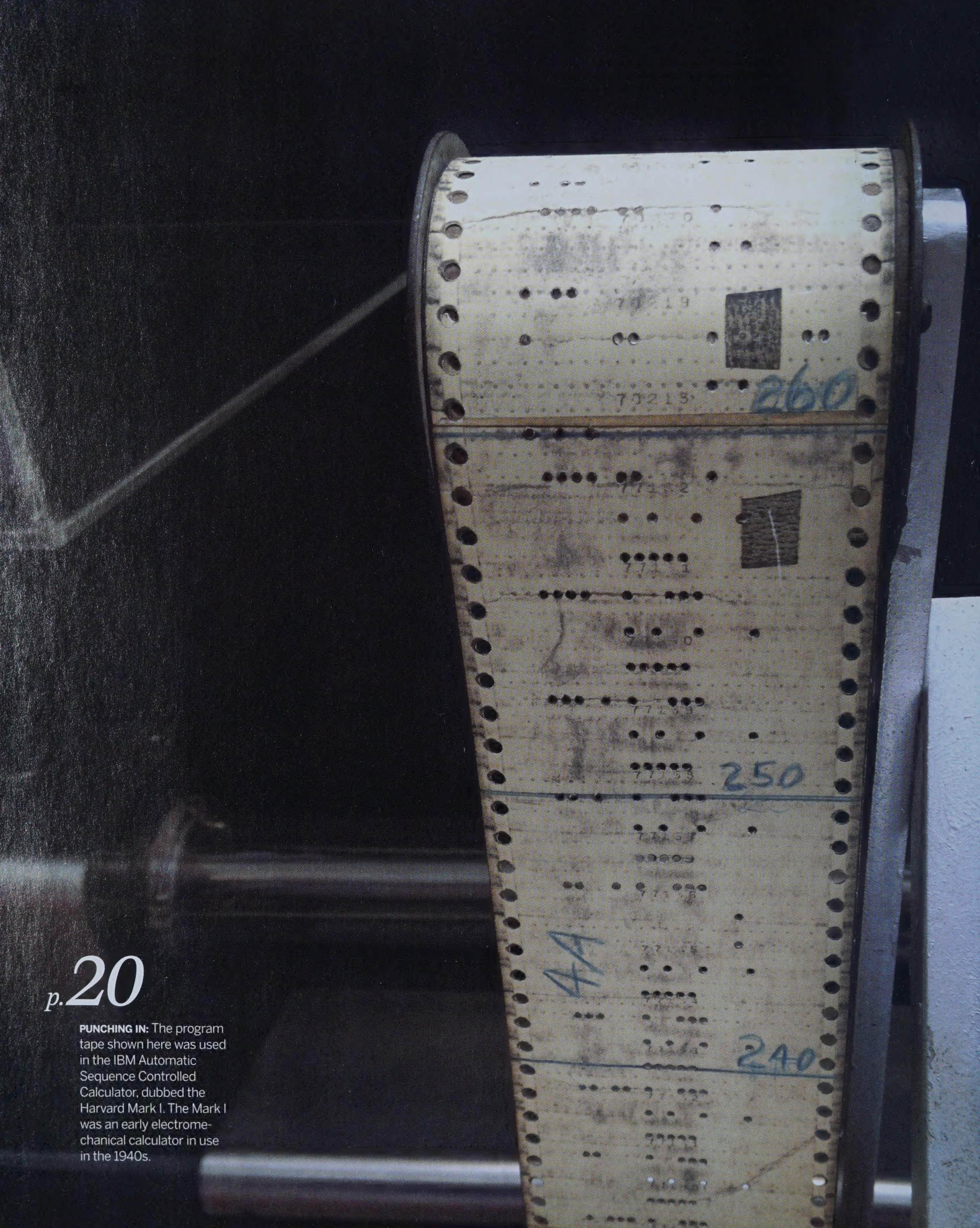


Artificial intelligence releases the power of patient data into the clinic

a sense of place

For nearly a century, students who come to HMS have lived in Vanderbilt Hall. The roll of residents tends to skew toward first-years; as students advance through the academic program, establish friendships, and become more comfortable with the rhythms of life as a medical student, they often seek accommodations in the surrounding community.

Although residents come and go, the rituals of life as a student, often far from home, abide. The daily mailbox check is one such ritual. Despite our culture's migration from committing words to paper, news that is folded, stamped, and addressed just to you is still valued. And how better to see if something awaits than by peering through the tiny window of your mailbox, assisted by the flashlight app on your mobile phone?



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PUNCHING IN: The program tape shown here was used in the IBM Automatic Sequence Controlled Calculator, dubbed the Harvard Mark I. The Mark I was an early electromechanical calculator in use in the 1940s.

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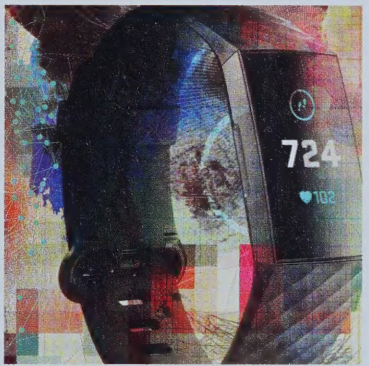

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ARTHUR REINHOLD/PD-USGOV-MILITARY-NAVY

The Power of Data, the Power of Change

BIOMEDICAL SCIENTISTS are riding a powerful wave of change in how we conduct our research.

Increasingly, biomedical science is being performed at the interface of wet-lab experimentation and high-powered computational and systems approaches. Artificial intelligence and machine-learning algorithms are becoming indispensable tools for virtually all forms of biomedical inquiry and are having profound effects on the practice of medicine.

This wave of change has been building for decades. In 1999, for example, the NIH's Biomedical Information Science and Technology Initiative noted that researchers were spending less time in wet labs gathering data and more time working in teams to harness the resources of computational technologies. "Digital methodologies," the initiative stated, "not just digital technology, are the hallmark of tomorrow's biomedicine."

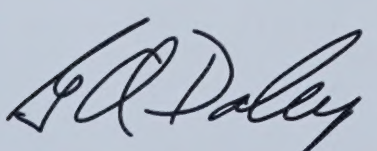
In the Blavatnik Institute at HMS, we have acted on this foresight and are adding our own energy to the movement. We have a strong record of integrating quantitative and computational approaches in our research. In our Department of Biomedical Informatics, teams of researchers are using data-driven approaches to better decipher radiologic images and better determine gene-informed treatments for patients with diseases such as cancer. In the Department of Systems Biology, researchers are drawing insights from math, physics, and computer science to illuminate the behavior of rogue cells in cancer and infection.

Artificial intelligence and machine-learning algorithms are having profound effects on the practice of medicine.

Our researchers in the Departments of Health Care Policy and Global Health and Social Medicine also are embracing computational tools. Their use of artificial intelligence and deep learning will one day result in tools that allow us to better analyze and form policies that will improve medicine and the delivery of health care.

We are developing novel initiatives that will extend our exploration of computational science in biomedical research. For example, our new Theory in Biology Fellows program, led by mathematician and Professor of Systems Biology, Johan Paulsson, will bring together physicists and computational and data scientists, allowing their work to be the glue between different programs and different modes of intellectual inquiry, while our therapeutics initiative is emphasizing the use of technology platforms to support collaborative efforts among our scientists.

These are exciting times for research as computational technologies provide biomedical researchers with exciting—and much needed—new tools. All of us who are dedicated to discovering ways to improve the health of all people, stem disease, and deliver care widely and equitably should embrace the power these tools bring to our work.



George Q. Daley
Dean of Harvard Medical School

HARVARD **medicine**

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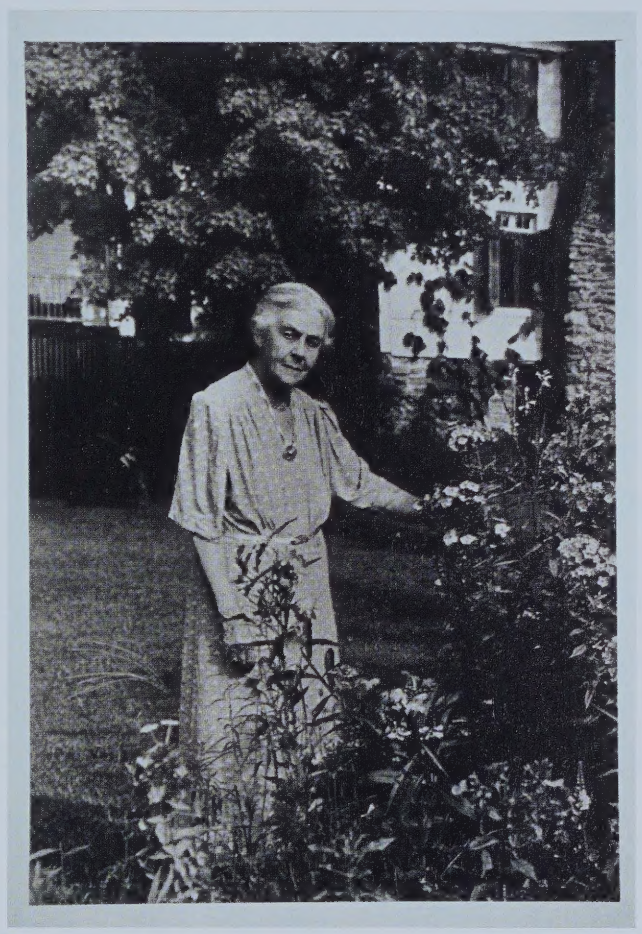
RANDY GLASS

“The result of Hamilton’s work was a thicket of laws and regulations aimed at protecting workers and, in some cases, the public.”



Alice Hamilton in the garden at her home in Hadlyme, Connecticut.

Indelible Mark

SINCE RESEARCHING AND WRITING the story on Alice Hamilton(*Harvard Medicine*, Autumn 2018), the good she accomplished has stayed on our minds. She was a phenomenal force; it is hard to forget her contributions.

To realize her desire to be of service to others, Hamilton took aim at the industrial organizations of her time. At that early period of the Industrial Revolution, business activity was focused on creating organizations at new dimensions of scale and complexity. Neglected was the well-being of workers; their work hours were terrible, and they were exposed to dangerous procedures, toxic chemicals, and other unacknowledged threats to health.

The result of Hamilton’s work was a thicket of laws and regulations aimed at protecting workers and, in some cases, the public. How ironic that the hundredth anniversary of her Harvard appointment coincides with a new industrial direction in which corporate efficiency seeks to trump her legacy of regulations aimed at protecting workers and the public by claiming those regulations are unnecessary and too complicated to follow. Doubtless, if she were here, she would set to work immediately to identify cases of deregulation that present challenges to the gains in safety and working conditions that she achieved in her long and vigorous life.

ELEANOR SHORE, MD ’55
MILES SHORE, MD ’54
NEEDHAM, MASSACHUSETTS

Ed: The Shores’ article on Alice Hamilton’s research, advocacy, and appointment to Harvard’s faculty was celebrated and shared during the installation of a bust of Hamilton in the atrium of the Tosteson Medical Education Center. The sculpture joins those of others who have made notable contributions to the School, medicine, and medical education.

Ahead of the Curve

WHILE TAKING A BREAK from my revision of an upcoming historical lecture on John Snow and the Broad Street pump, I perused the Autumn 2018 issue of *Harvard Medicine*. I was delighted to see Snow’s iconic map in your article “The Lay of the Land,” and the mention of its significance to the field of epidemiology. Your readers may be, as I am, even more fascinated and impressed by Snow’s use of a Voronoi diagram. (**https://plus.maths.org/content/uncovering-cause-cholera**).

In 1854, Snow drew a curve on the map you showed that represented the points where the pump was (like the 50-yard line on an empty football field and its relationship to the two goal lines) at equal walking distance to the next nearest water pump. For any person living within this curved figure, the Broad Street pump was the nearest water source. To better appreciate Snow’s genius (he was also a founding father of anesthesiology), it is important to recognize that he drew this curve fifty-four years before Georgy Voronoi created his eponymous diagram in 1908!

JOHN D. BULLOCK, MD ’68
WINCHESTER, MASSACHUSETTS

Ed: We thank Dr. Bullock for providing this fascinating information and giving added perspective to the work of John Snow. We also appreciated the fact that his letter has something in it for just about everyone: epidemiologists, mathematicians, cartographers, historians, medical anthropologists, and sports enthusiasts.

This cluster of colorized prostate cancer cells, imaged using scanning electron microscopy, shows cell bodies in blue, nuclei in pink, and cell extensions in yellow.

In Focus

RESEARCH to test the predictive value of prostate cancer screenings for Black men in the United States has found that a single baseline prostate-specific antigen (PSA) screening during midlife strongly predicts risk of total and aggressive cancer in members of this cohort for up to 12 years. The study, say HMS researchers at Brigham and Women's Hospital and Harvard T.H. Chan School of Public Health, is the first to address whether an optimized screening strategy with baseline PSA levels predicts prostate cancer in this population. U.S. Black men are more likely to be diagnosed with, and 2.5 times more likely to die of, prostate cancer than their white counterparts.

Preston MA, et al., *European Urology*, September 2018

NEUROLOGY

More clues found to serotonin's role in SIDS

RESEARCHERS INVESTIGATING what triggers sudden infant death syndrome are increasingly looking at the neurotransmitter serotonin and the brain cells that produce it. Serotonin-producing neurons have been linked to the regulation of breathing, and tissue samples from many infants who die of SIDS show abnormalities in those neurons.

HMS genetics researchers have indeed found that, in mice, abnormalities in serotonin-producing neurons not only accompany a subset of SIDS cases but could also contribute to premature deaths. In addition, their findings show that an acute loss of normal activity in serotonin-producing nerve cells blunts the body's ability to recover from interrupted breathing.

Their study provides evidence that young animals need properly functioning serotonin neurons to maintain normal cardiorespiratory function.

In conditions such as sleep apnea, when breathing temporarily stops, oxygen levels in cells can fall too low and carbon dioxide levels can rise too high. To restore healthy levels, the brain triggers a series of gasps and raises the heart rate, a process called autoresuscitation.

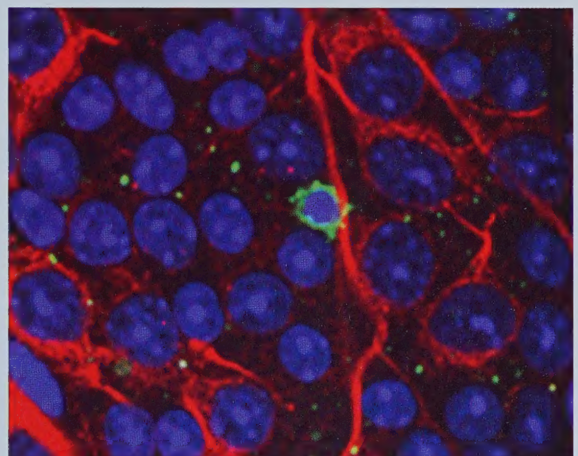
But heart-rate monitor readings in some infants support the hypothesis that this fail-safe mechanism doesn't always kick in, and its failure can lead to SIDS.

The researchers note that if it can be shown in their mouse model that serotonin-producing neurons play an active and necessary role in regulating breathing, heart rate, and the recovery response to apneas, these neurons could provide a plausible biological explanation for at least some SIDS cases. If replicated in human studies, the findings could eventually help improve screening tools to identify infants at higher SIDS risk.

Dosumu-Johnson RT, et al., *eLife*, October 2018

Immunology

Immune cells in the eye may contribute to progressive vision loss



Research in mice and humans has found that immune cells in the eye, developed after exposure to bacteria, contribute to progressive vision loss from glaucoma. The high pressure that marks the condition spurs an autoimmune response that attacks neurons in the eye. Glaucoma is a leading cause of irreversible blindness globally.

Chen H, et al., *Nature Communications*, August 2018

CLINICAL MEDICINE

Heart-healthy guidance for teens with type 1 diabetes

PEOPLE WITH TYPE 1 DIABETES are more likely to develop cardiovascular disease than those without diabetes. Their risks climb if there are signs of high blood pressure or unhealthy levels of cholesterol or triglycerides.

To help avert such risks in teens, HMS researchers at Joslin Diabetes Center have identified strategies that could help teens manage their health better.

The researchers say that health care professionals should offer teens realistic and specific guidance, beginning with basic information about their condition.

Providing teens with detailed personal guidance, including heart-healthy behaviors that can provide immediate benefits such as improving how they look and feel, is one way to approach conversations with teens. Adding details of how the disease will affect them directly—what their personal risk is, what specific foods and activities could help them—is another.

Using lessons learned from their work, the research team is now running a pilot study designed to encourage heart-healthy behaviors in teens with type 1 diabetes and additional cardiovascular risk factors.

Katz M, et al., *Pediatric Diabetes*, September 2018

CANCER

Evidence for aspirin's role against liver cancer grows

SEVERAL PAST STUDIES have suggested that the regular use of aspirin can reduce the risk of developing primary liver cancer, also called hepatocellular carcinoma (HCC). Recent research by HMS scientists at Massachusetts General Hospital has added strong new evidence for this.

The researchers analyzed data from two long-term epidemiologic studies and found that regular aspirin use—taking two or more 325-milligram tablets a week for five years or more—significantly reduced the risk of developing HCC, which is the second-leading cause of cancer death worldwide.

The researchers caution, however, that because regular use of aspirin carries the risk of increased bleeding, there is a need to directly study its effects in populations with established liver disease, a group already at risk for primary liver cancer.

While HCC is relatively rare, its incidence and its mortality rate in the United States has increased over the past forty years. The primary risk factor for HCC is cirrhosis, which can be caused by hepatitis B or C infection, alcohol use disorder, or nonalcoholic fatty liver disease.

HCC is usually diagnosed at a late stage, leading to an average survival time of less than a year. Aspirin is known to block the production of inflammatory lipids that can lead to liver injury, and while some previous studies have suggested that regular use could help prevent HCC, information on the optimal dosage and required duration of treatment had not been available.

In the current study, the research team compiled comprehensive health data col-

lected from a pool of more than 170,000 individuals since the 1980s.

Among the more than 133,300 participants—more than 45,800 women and 87,500 men—whose data were analyzed, regular use of aspirin led to a 49 percent reduction in the relative risk of developing HCC.

Among those taking aspirin for five years or more, the relative risk was reduced by 59 percent. If aspirin use was discontinued, risk reduction decreased over time and disappeared eight years after aspirin use was halted. Regular use of acetaminophen or nonsteroidal anti-inflammatory drugs like ibuprofen had no effect on HCC risk.

Simon TG, et al., *JAMA Oncology*, October 2018

AGING

Genes for fracture, bone mineral density linked

A LARGE INTERNATIONAL RESEARCH collaboration that included HMS researchers at the Institute for Aging Research at Hebrew SeniorLife has reported the first genome-wide association study of fracture risk. In addition to providing insight into the biologic mechanisms leading to fractures, the study reports fifteen variations in the genome that are related to the risk of suffering bone fractures.

Among the clinical risk factors for fracture assessed in the study, only bone mineral density showed a major causal effect on fracture. In addition, the study provides evidence against a causal effect of other proposed clinical risk factors for fractures, including diabetes, rheumatoid arthritis, and vitamin D levels.

The findings indicate that treatments aimed at increasing bone strength are more likely to be successful in preventing fractures than widespread supplementation of calcium and vitamin D or targeting other risk factors that were not found to mediate the condition.

Bone fractures affect more than nine million people worldwide every year. In this country, thirty-four million people have low bone density, putting them at higher risk for osteoporosis, a condition that leads to an increased risk of fracture, especially of the hip, spine, and wrist.

For the recent study, the researchers analyzed 185,057 cases of bone fractures and 377,201 controls drawn from the Genetic Factors for Osteoporosis Consortium, the UKBiobank Study, the EPIC-Norfolk study, and the biotech company 23andMe.

All of the fracture-associated genomic regions identified by the team were previously found to be associated with variation in bone mineral density, one of the most important risk factors for fracture. Based on this finding, the study team performed an additional analysis that used genetic information to determine causal relations between risk factors and disease outcomes.

The analysis determined that only two examined factors—bone mineral density and muscle strength—play potentially causal roles in the risk of developing osteoporotic fracture. In fact, the findings showed that the genetic factors that lead to lowered vitamin D levels do not increase risk of fracture; thus, vitamin D supplementation is not likely to prevent fractures in the general population. Although vitamin D supplementation is part of clinical guidelines, recent randomized controlled trials have failed to consistently demonstrate a protective effect against fractures.

Trajanoska K, et al., *BMJ*, August 2018

GENETICS

Tool predicts CRISPR's action in three cell lines

HMS INVESTIGATORS at Brigham and Women's Hospital, together with colleagues at the Broad Institute and MIT, have discovered that template-free CRISPR-Cas9 gene editing is predictable, and they have developed a machine-learning model that can predict insertions and deletions with high accuracy. The model can be used to edit and, in more than 50 percent of cases, predictably repair mutations related to three diseases in human cell lines: Hermansky-Pudlak syndrome, Menkes disease, and familial hypercholesterolemia.

Many genetic diseases arise from insertions and deletions that disrupt a gene's function, and accurately replicating or fixing these genes has long been a research goal. Conventional wisdom has held that the CRISPR-Cas9 tool randomly generates insertions and deletions in a gene unless researchers include a so-called repair template. This research team, however, found that, even without a template, one can predict which insertions and deletions are most likely to occur. At certain genomic sites, they found that a single mutation dominates. The team used the term "precise-50" to indicate when a single such mutation comprised more than 50 percent of all major editing products.

For this project, the researchers constructed a library of 2,000 Cas9 guide RNAs (gRNAs) paired with DNA target sites and used the library to train a machine-learning model. They found that the tool could predict deletions of varying lengths and single base-pair insertions with a high degree of accuracy in five human and mouse cell lines and predicted up to 11 percent of the precise-50 gRNAs.

The team confirmed the findings by using select gRNAs to correct mutations in cells collected from patients with genetic diseases that result when specific genes are duplicated. Hermansky-Pudlak syndrome causes blood clotting deficiency and albinism. Menkes disease results in copper deficiency. The team generated cells with the duplications found in patients that result in familial hypercholesterolemia, a disease in which LDL cholesterol levels are abnormally high. For all three diseases, the appropriate Cas9 and gRNAs corrected the mutation with high efficiency.

Shen MW, et al., *Nature*, November 2018

JNBPHOTOGRAPHY/ESSENTIALS/GETTY

HM INDEX: *IN THIS NATION, BETWEEN **20** AND **30** PERCENT OF PEOPLE **65** OR OLDER WHO FRACTURE A HIP DIE WITHIN **1** YEAR OF THE INJURY.*

Something Extra

A FIVE-YEAR STUDY of dietary supplement use in nearly 26,000 participants found that omega-3 fatty acids reduced heart attack rates by 28 percent but did not affect risk of stroke or cancer. Within the omega-3 group, reduction of heart attack risk was especially pronounced among Blacks, who made up 20 percent of the total participant pool. Although vitamin D did not significantly affect heart attack, stroke, or cancer incidence, it was linked with a 25 percent decrease in cancer deaths. The decrease began one to two years after participants began taking the vitamin. The study was conducted by HMS researchers at Brigham and Women's Hospital.

Manson JE. et al., *The New England Journal of Medicine*, November 2018

A colorized scanning electron micrograph of a cultured T cell that has a large number of exosomes budding from its surface.

Nasal Passage

GIVEN THAT BACTERIA are in just about every breath we take, how is it that our airways remain largely free of infection? Research by HMS scientists at Massachusetts Eye and Ear has provided an answer. According to their study, when cells at the front of the nose detect bacteria, they trigger TLR4, a receptor that stimulates the release of tiny fluid-filled sacs called exosomes. The exosomes not only contain an antimicrobial molecule that attacks the bacteria, but they also shuttle the protective antimicrobials from the front of the nose to the back of the airway, protecting other cells along the way.

Nocera AL, et al., *Journal of Allergy and Clinical Immunology*, November 2018

BASIC AND SOCIAL SCIENCE RESEARCH

A transformative commitment to human health

On November 8, Dean George Q. Daley, MD '91, announced that the School had received a multimillion-dollar commitment to benefit science initiatives that will transform human health.

IT IS WITH A GREAT SENSE OF EXCITEMENT that I announce that Harvard University has received a momentous $200-million commitment to benefit Harvard Medical School. This gift is from the Blavatnik Family Foundation. It will propel our shared mission to transform human health and advance our work in service to the world.

I join Harvard President Lawrence Bacow in expressing deep gratitude for this generous gift, which will fund a series of initiatives that will strengthen fundamental discovery at HMS, spur the next generation of precision therapies, and enable advances in data science.

Specifically, the gift will:

- *Fund a therapeutics initiative to advance novel approaches to the conceptualization, discovery, and development of new therapies.*
- *Spark fertile new intellectual communities by enriching the School's pool of scientific talent and integrating data science, computational and systems capabilities, and applications.*
- *Build bridges across disciplines and areas of inquiry through a robust community grants program to bring scientists together to solve pressing biomedical challenges.*
- *Launch the Blavatnik Harvard Life Lab Longwood, an incubator space on the HMS campus for early-stage, high-potential biotech start-ups.*

In recognition of this remarkable generosity, we are establishing the Blavatnik Institute at Harvard Medical School. This umbrella research organization will encompass and give unique identity to the pioneering work of our eleven basic science and social science departments.

Following the celebration of the gift from the Blavatnik Family Foundation, a banner announcing the formation of the Blavatnik Institute at HMS was unfurled on Gordon Hall.

The Blavatnik Family Foundation is a steadfast supporter of leading scientific, educational, cultural, and charitable institutions in the U.S., the U.K., and around the world. Led by business leader, entrepreneur, and philanthropist Len Blavatnik, MBA '89, the Foundation is known for its substantial commitments to advancing life-sciences innovation globally, such as the Blavatnik Awards for Young Scientists.

The Foundation's history of support at Harvard began in 2007 with the establishment of the Biomedical Accelerator Fund. In 2013, the Blavatnik Biomedical Accelerator at Harvard University was created, along with the Blavatnik Fellowship in Life Science Entrepreneurship at Harvard Business School.

Many HMS faculty members—including Ulrich von Andrian; Christophe Benoist; Ying Kai Chan, PhD '15; George Church, PhD '84; David Ginty; Diane Mathis; Lee Rubin; and Priscilla Yang—have received support from the Blavatnik Biomedical Accelerator to advance translational efforts in areas spanning cancer immunology, regenerative medicine, neuroscience, infectious disease, and reproductive medicine.

We are deeply grateful for this trailblazing gift and the promise it carries. This is indeed a new chapter in the history of Harvard Medical School, as we work together to pursue deeper insights into the fundamental mechanisms of living things, develop life-altering therapies, and reshape the course of human health.

noteworthy

A sea change in representation cheered by the HMS community

In the atrium of the Tosteson Medical Education Center sits a bust of Alice Hamilton, former physician, public health advocate, and member of the HMS faculty.

The likeness, unveiled to the HMS community during a ceremony in September, is the first sculpture to honor the contributions of a female member of the School's faculty. It is, according to Dean George Q. Daley, MD '91, a celebration not only of her accomplishments but of the School's values of diversity and inclusion. In addition, he said at the ceremony, "it is the first step of an initiative to refresh imagery and artwork at HMS."

"We will evolve our art so that it inspires and celebrates our great diversity," Daley said, "while paying homage to our past. We are committed to recognizing Alice and others who have contributed so much to our school and to the world, and who have been underrepresented in what we display in our halls."

In 1919, Hamilton (*fig. 1*) accepted an appointment as an assistant professor of industrial medicine at HMS. She became the first woman faculty member at Harvard and HMS, a breakthrough that came nearly three centuries after the School was founded. A pioneer in the field of toxicology, Hamilton was an expert in industrial and occupational health, a discipline she was instrumental in establishing. For her work in this area, she became the first woman to receive a Lasker Award.

With the help of the HMS Aesculapian Club and the Countway Library Center for the History of Medicine, a decision was made to commission a sculpture of Hamilton.

The work to renew campus artwork will be guided by the Arts and Cultural Representation Committee, led by Nawal Nour, MD '94, HMS associate professor of obstetrics, gynecology and reproductive biology at Brigham and Women's Hospital, and Dean for Students Fidencio Saldaña, MD '01, and composed of faculty, students, and staff.

New departments, leaders in basic science welcomed

As biomedical science evolves, so, too, does the leadership and structure of the entities that study it. Recently, the School welcomed three new chairs and one co-chair of basic science departments that study immunology, microbiology, and stem cell and regenerative biology.

The new Department of Immunology in the Blavatnik Institute at HMS will be led by Arlene Sharpe, PhD '81, MD '82 (*fig. 2*), the George Fabyan Professor of Comparative Pathology. A world-renowned immunologist and expert in T-cell regulation, Sharpe's work has yielded key insights into cancer's ability to evade immune surveillance.

Ann Hochschild, PhD '86 (*fig. 3*), the Maude and Lillian Presley Professor of Microbiology, will lead the new Department of Microbiology in the Blavatnik Institute at HMS. Hochschild is a leading expert in bacterial transcription and the biology of prions.

The areas of immunology and microbiology were previously housed in a combined department. In his announcement of the split, Dean Daley noted that the formation of the two academic units recognizes the depth and intellectual rigor of these scientific communities and acknowledges the complexity and critical importance of both disciplines in contemporary biomedicine.

The leadership changes in the Harvard Department of Stem Cell and Regenerative Biology serve to further recognize the multidisciplinary research and innovative teaching philosophy of the unit.

The new chair for the department is Paola Arlotta, with Amy Wagers serving as department co-chair. Arlotta, the Golub Family Professor of Stem Cell and Regenerative Biology at Harvard University, researches ways to aid neuronal regeneration, especially for neurodegenerative diseases affecting the cortex.

Wagers, the co-chair of the department and the Forst Family Professor of Stem Cell and Regenerative Biology at Harvard University, studies how changes in stem cell activity affect cellular homeostasis and repair throughout life.

fig. 1

fig. 2

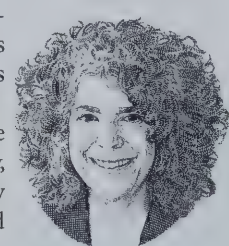


fig. 3

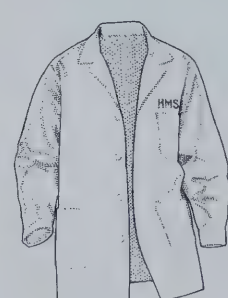


fig. 4

Incoming students learn of the challenges, joys of medicine

For many of the 200 members of the incoming Harvard Medical School and Harvard School of Dental Medicine Class of 2022, the start of their professional journey is the culmination of a lifetime of hard work and dreams.

As the new students received their white coats (*fig. 4*) during their first week of classes, they were cautioned that, while they will learn a great deal during the next four years, they will also face uncertainty and failure and that those experiences will inform their futures as physicians.

"You are going to learn so much more medicine in the forty or so years after medical school," said Edward Hundert, MD '84, dean for medical education. "You're going to learn the most from your patients."

Following a tradition begun in 2017, the students spent part of a day visiting Boston-area communities, traveling to nearly twenty different neighborhoods, many in underresourced areas. The idea is to help students develop an understanding of the social determinants of health.

The 165 medical students entering this year were selected from a pool of close to 7,000 candidates, according to Robert Mayer, MD '69, faculty associate dean for admissions.

Fewer than 900 of those candidates were invited for interviews and 3.4 percent were offered places in the new class, with 72 percent of those accepting. The students come from sixty-one different undergraduate schools, thirty-two U.S. states, and eight other countries.

Twenty-four percent of the class come from groups underrepresented in medicine. Ninety-five of the new students are female and seventy are male.

AI and Machine Learning

In the summer of 1956, a small group of academics gathered for a workshop at Dartmouth College. The meeting, billed as an attempt to "find out how to make machines use language, form abstractions and concepts, solve the kinds of problems now reserved for humans, and improve themselves," succeeded in giving birth to a field and a term: artificial intelligence. Since then, the field of AI, like the computing power of the tools it depends upon, has grown exponentially. In the pages that follow, we consider some of the ways that HMS researchers are contributing to that growth by crafting machine learning in service to medicine.

The Importance of Nuance

BY STEPHANIE DUTCHEN

Artificial intelligence may seem objective, but it's subject to human biases

In 2016, researchers in Heidelberg, Germany, built a sophisticated computer model, called a neural network, to identify melanomas based on clinical images. They fed it more than 100,000 photographs of lesions labeled "malignant" or "benign" and let it reverse-engineer its own methods for differentiating them.

The team then invited dermatologists from around the world to compare their diagnostic expertise to the model's. Provided with a new set of images and clinical data, the fifty-eight dermatologists, including thirty experts, from seventeen countries accurately diagnosed 88.9 percent of the melanomas and 75.7 percent of benign moles. The neural network detected 95 percent of the melanomas and 82.5 percent of the moles.

When the study was published in *Annals of Oncology*, it was hailed as another example of the promise of artificial intelligence in medicine. What remained other than to train the model on more complex cases and debate whether and how to one day incorporate such a tool into clinical practice?

Yet, down in the limitations paragraph of the paper, a problem became apparent: More than 95 percent of the images used to train the model depicted white skin.

If the model were implemented in a broader context, would it miss skin cancers in patients of color? Would it mistake darker skin tones for lesions and overdiagnose cancers instead? Or would it perform well?

To ensure that AI applications provide the greatest benefit while doing the least harm, it's essential to acknowledge that algorithms, like the people who construct them, use them, and gather the data they analyze, can be biased—and that steps must be taken to identify and correct such biases.

An all-purpose tool

With its increasing power to analyze enormous data sets and make accurate predictions, artificial intelligence is poised to sweep through medicine. It has made rapid progress in certain clinical tasks, especially in analyzing images. Recent studies show that algorithms can rival or even outperform experienced clinicians in detecting abnormalities ranging from diabetic retinopathy to pulmonary tuberculosis. Models also can predict with startling accuracy outcomes such as an admitted patient's length of stay, likelihood of in-hospital death or unplanned readmission, and diagnosis at discharge.

Meanwhile, algorithms designed for basic science are making headway in difficult endeavors such as extrapolating protein structure and function from gene sequences and predicting the health effects of gene variants. In the translational realm, computational tools are learning to prioritize potential drug targets, predict drug

activity and toxicity, discover new drugs and disease biomarkers, and unearth additional uses for existing drugs.

These models and others have the potential to extract new insights from data sources too vast for human minds to decipher; generate more consistent diagnoses and prognoses and deliver them faster; and save money, resources, and time that health care practitioners, for example, can spend more meaningfully with patients. For now, however, most models remain in various stages of development with a focus on improving their safety and accuracy.

Tread cautiously

"AI is smart in many ways, but it is subject to the principle of 'garbage in, garbage out,'" says Kun-Hsing Yu, an instructor in biomedical informatics in the Blavatnik Institute at HMS. "If the input has a systemic bias, the model will learn from that as well as from actual signals."

Biases can enter at any stage of AI development and take many forms, from analysis of skewed or insufficient data to the confirmation bias that leads a radiologist to agree with an algorithm's false-negative findings and thus miss a lesion in a patient's x-ray. Demographic biases alone span gender, race and ethnicity, age, income, geographic location, primary language, lifestyle, and BMI; failure to detect any of these when building or implementing a model can replicate or exacerbate disparities in patient care.

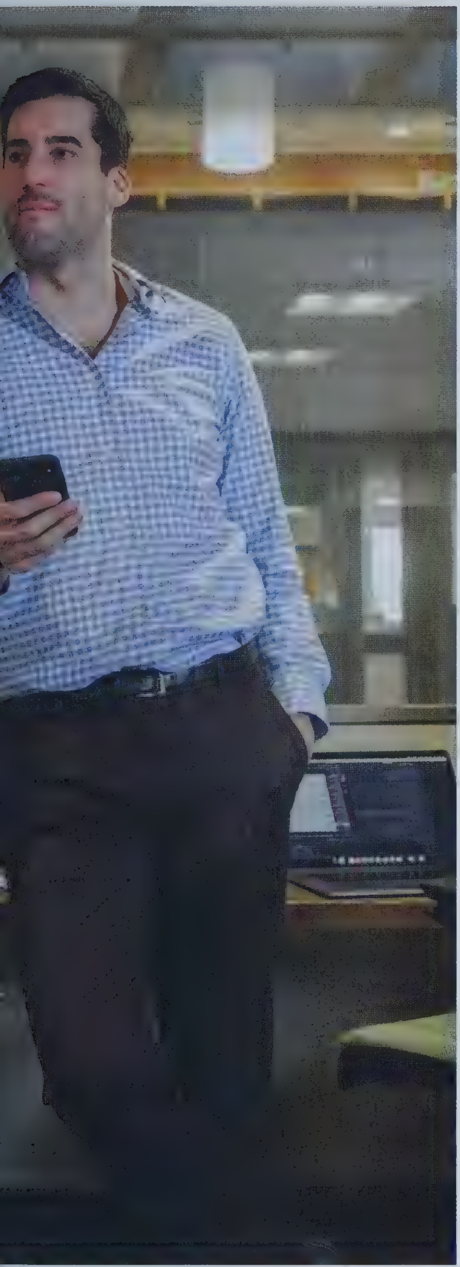
"If you're training any algorithm to make decisions, you're incorporating the structure of the way things work today or how they worked in the past," says Brett Beaulieu-Jones, an HMS research fellow in biomedical informatics. "If you're not controlling for and getting ahead of biases, you'll perpetuate them."

Scientists Kun-Hsing Yu (above) and Brett Beaulieu-Jones work to remove or identify bias in medical artificial intelligence.

Biases may often be unintentional, but they could also be introduced deliberately. Some researchers point out that AI applications in hospitals could be designed to prioritize so-called quality metrics or make recommendations that financially benefit the AI manufacturer, a drug company, or the institution without clinicians' or patients' knowledge.

Overlooking bias in medical AI invites serious consequences. Recommendations based on biased models or inadvertent misapplications of a model could result in increases in illness, injury, and death in certain patient populations. Biased models could waste time and money in the lab and lead researchers on wild-goose chases when they're trying to translate fundamental discoveries into new treatments. And they could erode what fragile trust the profession or the public may place in medical AI.

"Evaluate how representative your data set is. Perturb the data, see if your model is sensitive to demographics."



Just ask

AI researchers really buckled down to address the problem of bias within the past few years, say Yu and Beaulieu-Jones. Groups such as the AI Now Institute at New York University, a research center investigating the social implications of artificial intelligence, have sprung up to hold the field accountable for addressing issues such as bias and inclusion.

To date, the United States has no requirements to test for bias in AI and no standard for determining what bias is or whether it exists. Thus, researchers across disciplines are on their own when establishing best practices and raising awareness of pitfalls.

To date, the United States has no requirement to test for bias in AI and no standard for determining what bias is.

To spot bias, they agree, people first need to be aware that it may exist. That requires correcting misconceptions that machines are objective and infallible as well as admitting to the possibility of individual, institutional, professional, or societal biases.

The first place to look for bias is in the data sets used to "teach" AI models before those models can apply their lessons to new cases. Since AI has a bottomless appetite for data, researchers are realizing they must ensure that the data are of the highest quality and fully represent the patients, or the proteins, the resulting model will be applied to.

"If you think your data set is perfect and you don't ask what can be wrong, what are the biases, you create more bias," says behavioral scientist and lawyer Paola Cecchi-Dimeglio, a senior research fellow at Harvard Law School and the Harvard Kennedy School. "But if you pause, you can prevent the reinforcing of bias."

AI developers and those who use the tools they build can ask where the data originated and what biases it might contain. Was information pulled from a public repository of genome sequences? If so, chances are that more than 80 percent of that DNA came from people of European ancestry, increasing the likelihood that a model trying to uncover disease-associated gene variants would reach faulty conclusions when applied to other populations.

"Evaluate how representative your data set is," says Yu. "Perturb the data, see if your model is sensitive to demographics."

If a weakness is detected, researchers can gather more-robust data sets. Crowdsourcing, for example, can provide new data that includes groups underrepresented in the original samples. The Heidelberg research team ended up opening its skin-cancer image banks to contributions from around the world.

Whereas now "there's almost an incentive to have a homogeneous data set to achieve greater statistical power," funders and policymakers could help prevent bias by supporting researchers in collecting more diverse samples, says Beaulieu-Jones.

An algorithm of one's own

Those who can't feasibly generate new data still have options. Some researchers can pull from multiple data sources to try to reveal or balance each one's biases, says Beaulieu-Jones. Some may be able to start training their model on a large, less representative data set, then fine-tune it on a smaller, more specialized one. Others might perform statistical operations that can improve imperfect data, such as weighting samples differently or using estimated values to compensate for missing data, a method called imputation.

What data scientists call "missingness" poses one of many challenges for those seeking to tap the firehose of information

The National Center for Health Statistics monitors the adoption of electronic health records by individuals and groups that deliver health care. In a fact sheet issued in May, it reported that in 2015

86.9 percent

of office-based physicians used some type of EHR, an increase from

34.8 percent

in 2007. NCHS data are used to study care delivery, services rendered, and patients served across diverse settings.

collected in electronic health records. In one study, Beaulieu-Jones and colleagues found that the EHRs for most participants in a group of clinical trials for amyotrophic lateral sclerosis (ALS) were missing 50 percent of relevant data points. Not only do patchy data hamper analysis, data that are systematically missing can drive bias. If, for example, an algorithm is programmed to maximize accuracy by ignoring incomplete records: the patients with fewer tests or whose medical histories are scattered across multiple EHRs often are those with mental health conditions or lower incomes.

That's where imputation can help. It's a specialty of Beaulieu-Jones's, who, with HMS colleagues, considers EHRs a more demographically comprehensive source of data about neurodegenerative diseases than clinical trials, which trend white, male, young, and affluent. In the ALS paper, he found that conducting imputation to bolster EHR data and reduce bias didn't harm the algorithms' ability to predict patients' disease progression.

In a separate study in *JMIR Medical Informatics*, he and colleagues compared twelve imputation methods using the EHRs of 602,000 patients from Geisinger Health System in Pennsylvania. The team was then able to advise researchers with less technical expertise on how to assess missingness in their own data and when and how to conduct repairs, such as imputation, on EHRs. The team's code and methods are publicly available.

There's another opportunity to catch biases after an algorithm has processed the data and delivered its conclusions. Machine-learning algorithms—those that develop their own prediction rubrics from the information they're fed—identify associations, only some of which are causative. As with any research endeavor, Yu and others stress, it's critical to think about confounding factors when building and using AI models. In EHRs, potential confounders abound in the guise of not only missing data but also patient zip codes, differences in which patients get lab tests, diagnostic codes that are chosen for insurance reimbursement, and date of visit standing in for date of onset of condition.

Paola Cecchi-Dimeglio uses artificial intelligence to aid organizations in their efforts to improve diversity inclusion.

And that's not even getting into the fact that race, gender, and biology aren't as clear-cut as traditionally defined.

"We need to do more careful analyses and more causal analyses," says Yu. "AI is so complex that we may need a more sophisticated understanding of, and language for, cause and effect."

If all other attempts to control for bias fail, say Yu and Beaulieu-Jones, researchers and AI developers can at least state the study's limitations so others can act accordingly.

Describing the elephant

It's even harder to assess bias when details are lacking about data provenance or when algorithms are either too complex to understand or concealed by the designer for proprietary reasons.

"Black box" algorithms that prevent insight into how tools make decisions are a major concern in the AI field today. Some turn to legislation and advocacy. Cecchi-Dimeglio joins many others in wanting more regulation in this country around ethics and transparency. Samuel Volchenboum, an associate professor of pediatrics and director of the Center for Research Informatics at the University of Chicago, argued in a coauthored *Harvard Business Review* article that government institutions such as the U.S. Department of Health and Human Services need to prevent medical data sets from being privatized, as credit scores were.

Others, including Beaulieu-Jones and Yu, are trying to pry open black boxes to uncover hidden biases or other issues that could affect patient safety or research quality. In cases where they can't peek inside, they look for other ways to gauge how the algorithms might be operating.

"Opening up the black box is hard," says Yu. "Without opening it, we try to at least grasp the basic concepts, such as what the algorithm is paying attention to."

Yu is part of an international research consortium training machine-learning algorithms to interpret histology slides. The group's goal is to investigate the dogma that pathologies present in consistent ways at the cellular level across humanity. For an AI application that interprets visual data, as this one does, he might apply what's known as an attention map to discover whether the algorithm spends more time analyzing the area of interest, such as a tumor—or something else.

"It's not just a gut feeling; this is what the data tell you. We all are biased, but you're not telling someone that. You're able to shift to a productive conversation."

"An algorithm might accurately distinguish cats from birds, but it might be doing so by identifying trees in the background, because birds are more often found outside," says Yu. "You want to know how it's arriving at its conclusions."

Similar methods prove useful even when the inner workings of AI applications aren't secret. Many neural networks consist of more than one hundred so-called layers that together process tens of millions to hundreds of millions of parameters, says Yu. He might look at the inputs and outputs between the first few layers to see how they detect lines, edges, circles, and dots in an image, but the higher-level features remain out of reach.

On the opposite end of the spectrum from black-box engineering, many AI developers practice open-source coding. Transparency, however, doesn't mean bias is automatically identified or removed, cautions Beaulieu-Jones.

Multiple choice or essay

Accessible or opaque, simple or convoluted, the key to reducing AI bias is to test, test, test. Algorithms must be built and tested in diverse environments, say UCSF researchers in an article in *JAMA Internal Medicine* in November. Chief among the AI Now Institute's exhortations is to treat new AI applications like drugs entering the market, ensuring that they undergo rigorous scientific testing followed by continuous monitoring of their effects.

The good news is people don't need a degree in computer science to use AI responsibly. A basic education in how algorithms work can help users understand where bias might creep in, how to ask an AI application the right questions, how to apply the results in appropriate ways, and when to use or forego a particular piece of software in their work. Along with Yu's and Beaulieu-Jones's work to demystify aspects of AI, high-level organizations, including DARPA, are funding projects to raise user literacy.

The lift from a rising tide

Data sources and testing environments aren't all that can be diversified in the pursuit of reducing bias. Creating more interdisciplinary teams that mix computer scientists, bioinformaticians, clinicians, researchers, and epidemiologists would raise the likelihood of unbiased AI results, wrote the UCSF team. Others call for broadening the demographic diversity of the teams that collect data and recruit for studies, and for funding agencies to more equitably award grants to such researchers. The teams that build AI tools could use improvement as well; the technology sector lags behind other industries in diversity, according to the U.S. Government Accountability Office.

Cecchi-Dimeglio uses AI when she consults with organizations, including those in the health care and pharmaceutical industries, to improve diversity inclusion. She has found that her scientific approach goes over well in the medical arena because it begins with data analysis and evidence-based decision making, then moves to what she calls "nudge" interventions: testing changes one at a time and measuring the results until outcomes improve.

"It's not just a gut feeling; this is what the data tell you," she says. "We all are biased, but you're not telling someone that. You're able to shift to a productive conversation."

Cecchi-Dimeglio isn't the only one turning to AI to reduce bias in medicine. In September, Google released an open-source, visually based algorithm called the What-If Tool that allows users to assess the fairness of machine-learning models without needing to write code; Microsoft and IBM report that they are also working on automated bias detectors. More broadly, Beaulieu-Jones points out that since algorithms learn from current practice, they can surface existing biases. "That's one area where AI can be of help," he says.

The good news is people don't need a degree in computer science to use AI responsibly.

There are even murmurings about training algorithms on human ethics alongside technical tasks. IBM says it is working to incorporate "computational cognitive modeling, such as contractual approaches to ethics," into algorithmic decision making.

How good is good enough?

As medical AI evolves, the community faces difficult questions. Who decides what is fair? How much bias is acceptable? Do algorithms need to be perfect, simply better than people, or merely as good?

AI models that perform as well as or better than an average practitioner could benefit regions that are short on specialists, wrote Yu and colleagues in *Nature Biomedical Engineering* in October. Minimizing algorithmic bias would be critical for ensuring that resource-poor communities don't get handed off to algorithms that provide substandard care.

Experts emphasize that the end game for AI isn't to replace clinicians, researchers, or other human specialists. Nor could they, says Yu, who rests easy knowing that physicians will always have empathy and human touch on their side.

"As an MD by training, I don't want to be replaced by AI," he says. "But I'm not worried. It's more like doctors who don't use AI will be replaced by those who do." HM

Stephanie Dutchen is a science writer in the HMS Office of Communications and External Relations.

In 1990, administrators realized that the National Residency Match Program was unfairly handling couples looking to complete their medical residencies together. Because the algorithms hadn't been updated even as unions among medical students were becoming more common, they prioritized the higher-ranked partner's top choice rather than searching for middle ground.

Researchers are building an artificial intelligence system that can mimic human clinical decision making

One Giant Step

BY EKATERINA PESHEVA AND ANN MARIE MENTING

Andrew Beam

KATHLEEN DOOHER AND MATTIAS PALUDI

You're a first-year medical student and Step 1 of three United States Medical Licensing Examinations looms. Study drills include everything from anatomy to physiology, aging to immunology. Test prep books are pored over, the content in medical texts is boiled down to flashcards, and an electronic library of an estimated 20,000 of those cards, assembled by other med students over more than five years, is being scoured and its annotated sample exam questions analyzed.

The new year dawns and with it comes the posting of the USMLE scores. You've earned a 272. You breathe a sigh of relief.

At the Department of Biomedical Informatics in the Blavatnik Institute at HMS, however, more studying is in order. Not by human students, but by a "proto-med student."

An algorithm.

"We've been providing the algorithm with information that is increasingly complex, much like what a first-year medical student would face," says Andrew Beam, a research associate in the department and leader of the team that's been developing the artificial neural network. "We started by providing it with the content from basic science textbooks, moved to scientific literature, worked to increase its high-level vocabulary, introduced more targeted material, then started providing it with actual test prep material."

"Like a medical student," adds Beam, "artificial intelligence needs to begin with a broad foundation of knowledge so that it has a rough understanding of what the pieces are and a loose understanding of how they all fit together. If you just jump into the test prep material, everything looks random to the algorithm; it has no understanding of relationships. It has no context in which to make connections."

Beam estimates that his team will have the algorithm ready to test for next year's Step 1 exam. Then the team will further develop the artificial neural network so that it mimics human clinical decision making and performs on a par with a second-year medical student. They then will test it with the Step 2 exam, which assesses clinical knowledge.

Long term, the team hopes to evolve the network to achieve the diagnostic level of a fourth-year medical student, capable of analyzing clinical scenarios and applying clinical reasoning.

Building proto students was not always Beam's career goal. As an undergraduate computer science major, he had his sights on a career as a systems engineer in Silicon Valley. Then, in his junior year of college, he took a course in artificial intelligence.

"It blew my mind," Beam says. "It was the coolest thing—an awesome mix of philosophy, mathematics, and computer science. We pondered really fundamental questions about humanity and intelligence, everything to make an undergrad go, 'Whoa, dude!' "

Beam pursued a doctorate in informatics and now develops data-driven models that improve decision making in health care. He works to create artificial intelligence systems capable of sifting and interpreting the avalanche of data that has been spawned by research in a variety of clinical specialties over the past twenty years.

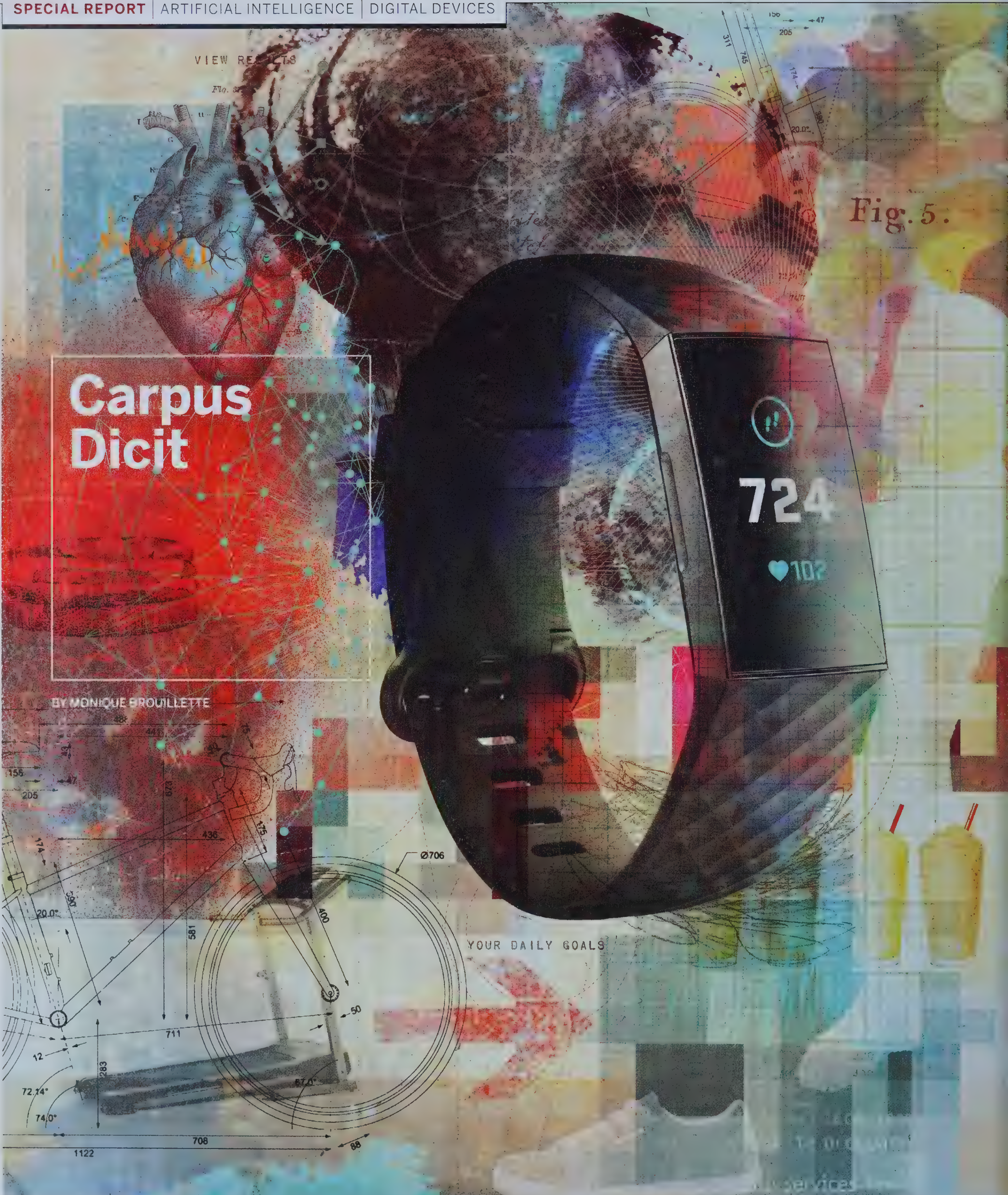
Recent research has demonstrated that big data can inform diagnostic algorithms that perform as well as—in some cases, better than—physicians. Some forecast that artificial intelligence will help alleviate clinician shortages while also improving access to diagnostic care for people living in remote or underserved geographic areas.

"The success of our proto-med student project would be a sort of milestone marker for research that applies AI to medical information," says Beam. "I also think there are some natural translational opportunities for a system that can answer general medical questions. It could be used as either a clinical physician-support tool or maybe even a type of patient-facing tool."

"I think this could have tremendous application in either the developing world or parts of the United States where health care services are not readily available," he adds. "It's not about AI versus MD, but MD enhanced by AI." HM

Carpus Dicit

BY MONIQUE BROUILLETTE



Wrist-worn digital devices promise to help people manage their health. It's an offer that may have strings attached

Amy Newell says she had a breakthrough because of a mobile phone app.

Several years ago, the 43- year-old software engineer was diagnosed with bipolar disorder and has since been trying everything she can to manage the crushing symptoms.

"Unfortunately, they were resistant to medication," she says.

Seated in a coffee shop, Newell pulls out her phone and scrolls to find the app that tracks her daily symptoms. A calendar appears with about half the days filled with little notes about mood, medications, diet, and exercise. These are all useful data for Newell when she faces difficult treatment decisions. She recalls how this past summer she used the app to track her mood in response to drinking alcohol. Her doctor had been urging her to stop drinking because of potential interactions with a medication, but she resisted. After curbing her drinking for a month, and tracking the results on her app, she found that alcohol was indeed a major precursor of depressive symptoms.

Reflecting on this breakthrough in a recent paper in the *Journal of Medical Internet Research*, Newell wrote, "My mood data during what is usually my worst month, July, finally convinced me that significantly limiting my alcohol use results in more stability. This is a lesson I was not remotely interested to hear from my psychopharmacologist, but the data, annoying though it was, did not lie and had no agenda."

Newell is one of a growing number of patients who manage their chronic health

John Torous is deeply involved in an American Psychiatric Association initiative to evaluate mental health apps so that consumers, patients, and mental health clinicians may make more informed decisions when choosing such apps.

JOHN SOARES

conditions with the help of smartphone apps and wearable digital devices. An estimated 250,000 mobile health apps exist on the market today, doing everything from tracking steps and calculating insulin doses to promising to support meditation practice and boost cognitive function. Given the size of this market, it is not hard to imagine a future in which your phone could warn you about potentially deadly conditions such as atrial fibrillation or help you manage medications.

Even health insurers are integrating these devices into their programs. In 2017, United Healthcare, a leading insurance company in the United States, announced partnerships with Fitbit, Garmin, and Samsung, makers of popular wrist-worn activity trackers, which would allow members to receive financial incentives by logging a greater number of steps each day.

A whole suite of tools is now available to help people manage their health. But this fast-moving, commercially driven trend remains largely outside the oversight of the health care regulatory establishment. Instead, companies often are validating their own products, emphasizing product usability and "stickiness" over data privacy and efficacy considerations.

Useful? Perhaps. Accurate? Perhaps not.

Earlier this year, Fitbit Inc., the company that makes the Fitbit wearable activity trackers, agreed to a settlement of a class-action lawsuit filed in 2016 by the State of California because of technical problems with the heart-rate sensor for two versions of its device. Researchers at California State Polytechnic University found that, during moderate and high-intensity exercise, the devices underestimated heart-rate readings by 15 and 22 beats per minute, on average, when compared to electrocardiogram readings. Such an error range is potentially dangerous, especially if the wearer uses the device to determine maximum heart rate during exercise. A 2017 study by scientists at the University of Wisconsin also found inaccuracies for the two devices studied by the California researchers and for wrist-worn activity trackers by two other manufacturers.

All such activity trackers measure heart rate by emitting a beam of LED light onto the skin on the inside of the wrist. Some of the emitted light is absorbed; some is reflected back. The device senses differences in light reflection that occur as the heart beats and sends blood pulsing through the arteries, causing a change in volume. But the variation in reflection is very small and can be overpowered by changes in light reflection resulting from movement. If a person is jogging and jostling around, for example, the heart rate monitor can miscalculate or even shut down altogether.

"It is important to realize that, although many apps appear useful, the actual evidence for clinical efficacy is nascent," says John Torous, MBI '18, an HMS instructor in psychiatry and director of the Division of Digital Psychiatry at Beth Israel Deaconess Medical Center. "I think we have to demand high-quality evidence." Torous is involved in an American Psychiatric Association effort to evaluate mental health apps and aid consumers in making informed decisions.

Out of nearly fifty apps designed to calculate insulin dosage, about 70 percent risked recommending an inappropriate dosage.

When it comes to questionable accuracy, activity trackers are not alone. A few years ago, insulin-dose calculator apps came under scrutiny. Patients with diabetes need to calculate insulin doses daily, and a number of apps have been developed to make this task easier. Researchers at Imperial College in London, however, found that out of nearly fifty apps designed to calculate insulin dosage about 70 percent risked recommending an inappropriate dosage. Roughly 90 percent of them lacked user validation to ensure that the data entered was correct—allowing mistakes that could lead to dangerous medication errors.

The high price of free

A few years ago, the United Kingdom's National Health Service opened a library containing a collection of mobile health apps that had to meet high standards of privacy. Inclusion of an app in the library was meant to assure consumers that sensitive health data would not be mishandled. Software developers were required to answer a series of questions regarding their security protocols; the questions explored whether the apps would meet the NHS's medical privacy standards.

A review in 2015 by researchers at Imperial College, however, found that many

"It is important to realize that, although many apps appear useful, the actual evidence for clinical efficacy is nascent."

of the apps stored medical data in ways that left the data vulnerable to interception. Nearly 20 percent of the apps had no privacy standards at all. Two-thirds of the apps sent identifying information over the internet without encryption, and nearly 80 percent of those had a policy on sharing data that lacked documentation about encryption practices. Four apps transmitted both health and identifying information without encryption.

The NHS example underscores the difficulty of keeping health data secure in a market where personal data drive profits.

"Apps are free or low cost because you're paying with your personal health data," says Torous. "The business model right now is your data."

Joseph Zurba, the information security and IT compliance officer at HMS, reviews the security of apps and wrist-worn digital devices used in HMS research studies. He thinks that securing digital health technology is more difficult than securing traditional medical record data because digital records face two constantly evolving threats: hackers and malware. He points to the data breach earlier this year at My Fitness Pal, a popular fitness-tracking app. In that breach, 150 million accounts were compromised, with the hackers making off with user names, scrambled passwords, and email addresses. Zurba says that balancing data privacy with the data collection potential of these devices is a complicated dance.

"We certainly can't say 'Never use these devices,'" says Zurba. "They can be very useful from a research perspective." Zurba points to the Apple research kit as a tool that can gather data on such things as how many steps you take, the length and cadence of your stride, and the number of flights of stairs climbed. When the data are combined with, for example, heart-rate data gathered from a wrist-worn digital device, he says, you have a wealth of data for use in research.

To help secure participant data on such devices, Zurba has come up with creative workarounds: During one study, he asked research participants to create email accounts using false names and birthdays in order to protect their true identity during storage with third-party services.

For I. Glenn Cohen, the James A. Attwood and Leslie Williams Professor of Law at Harvard Law School, the degree of worry over our data should vary depending on which data are being considered. When consumers are worried about losing data collected from their tracking devices, he urges them to maintain perspective. If, however, they are using apps that handle more sensitive information, like the genetic data that life insurance companies request to determine health risks, he believes ample caution is warranted. While there are laws that prevent employers and insurers from discriminating against people based on their genetic profiles, most states still allow life insurers to request genetic data if they are available.

Technology now evolves faster than the regulatory bodies that govern it.

"The kind of data you're generating with Fitbit and the like are unlikely to be usable at the individual level," says Cohen. "Companies are really interested in aggregate information. But when you talk about genetic information, I think people should be going into it with their eyes open."

Health apps and wearable digital devices are not regulated under the Health Insurance Portability and Accountability Act, which governs patient privacy in clinical settings and with insurers. These companies can therefore provide workers with health apps and wearable digital devices and sell the data they gather electronically.

But some still worry about the possibility of health insurance companies denying coverage for unhealthy habits and underlying conditions discovered through apps and wearable digital devices. If the preexisting conditions clause is removed from the Affordable Care Act, it is conceivable that collected data that reveal an underlying condition could be used to deny coverage.

A control issue

Technology now evolves faster than the regulatory bodies that govern it. One agency confronting the outcomes of this evolution is the U.S. Food and Drug Administration. Unlike traditional hardware-based medical devices, products that occupy the digital health technology space are often software-based. Keeping up with the pace of software development—and

Dick Tracy, the chisel-jawed, straight-arrow plainclothes detective who debuted in 1931 in the eponymous comic strip created by Chester Gould, is as well known for the technology he used as for the yellow fedora he wore. Some of the gadgets Tracy used are no longer just the stuff of imagination: his electronic telephone number pick-up tool is today's caller ID, while his two-way wrist radio, first seen in the strip in 1946, is a predecessor of the mobile phone—and the model for the two-way communication device that watches may one day become.

JOHN SOARES (OPPOSITE); MATTHIAS PALUDI

the innovation in digital health technologies that the FDA seeks to foster—has led the agency to an innovation of its own: the Software Precertification (Pre-Cert) Pilot Program, launched in 2017. According to the FDA, the program will "help inform the development of a regulatory model to assess the safety and effectiveness of software technologies without inhibiting patient access to these technologies." The program addresses a product category called SaMD, software as a medical device.

At its simplest, the new program would certify companies rather than individual products, and, much like the Transportation Security Administration's program allows preapproved passengers expedited security checks, would allow precertified companies a faster route to FDA clearance. Apple, Fitbit, and Samsung are among the nine companies currently participating in the pilot program.

Some consider the FDA's move to be controversial, especially if it means products will not need to show research that indicates actual health benefits for consumers. Three senators, including Elizabeth Warren from Massachusetts, have sent a letter to the FDA questioning whether the program will allow companies to essentially self-regulate.

Torous says the program is a novel approach, but "there are still many questions about how it will actually work and even if it will actually work in practice."

Dan Webster is one of those reassured by the FDA's involvement in software. Webster, a principal scientist for digital health at Sage Bionetworks, a nonprofit that builds and uses collaborative tools to support the integration of data science into biomedical research, is the scientific lead on the digital health effort at the All of Us Research Program. The program, launched in 2016, is an element of the Precision Medicine Initiative in the National Institutes of Health. Its goal: to enroll one million people living in the United States; collect data on their health, demographics, genomics, and behavior; and, ultimately, make that data available to medical professionals, researchers, and patients who seek to work collaboratively on making health care decisions.

"The All of Us program was designed with patients as active partners from its inception, full transparency in its approach and data collection, and clear privacy standards that place participants in control of their data and how it is shared," says Torous, who is also an adviser for the arm of the project focused on designing a smartphone mood-tracking app.


Joseph Zurba

Mobile health devices are earning a place in our health care system.

The program includes the use of a variety of apps and wearable digital devices to collect exponentially more, and more granular, data than clinical visits alone would.

Webster says the privacy policies at All of Us are still being formed, and developers will carefully consider many precautions to ensure participant privacy. One thing they are considering, he says, is masking data like latitude and longitude. If the All of Us researchers need location information in order to study the effects of, say, airborne particulate matter, they might collect only the first three digits of a zip code to make the geographic data less identifiable. He notes that the privacy policies and protocols for All of Us are posted online.

Medical applications like the one that helped Newell are just the beginning. Mobile health devices are earning a place in our health care system, offering patients and researchers the opportunity to gather vast amounts of data on a scale and granularity never before attainable. While these apps will likely be used in the clinic, the toll they might exact on patient safety and privacy remains to be determined. HM

Monique Brouillette is a Massachusetts-based science writer.

The ability to use vast amounts of medical data for clinical decision making is reshaping patient care

“If you think about a doctor’s job,” says Ziad Obermeyer, MD ’08, “making a decision for even one patient is a big data challenge.” Doctors must process an enormous flow of information, he explains, beginning with “the patient and her prior care—and all the data that accompany that, while also incorporating the research literature that is growing every day.”

For centuries, a physician’s first source of data has come from the clinical conversations that form the heart of the doctor-patient relationship. Think of this as the fine art of listening. The information from that conversation is documented in medical records as notes, forming the basis of medical reasoning and clinical decision making.

With the volumes of data being captured in biomedical laboratories and through electronic health records, making well-informed clinical decisions is becoming increasingly challenging.

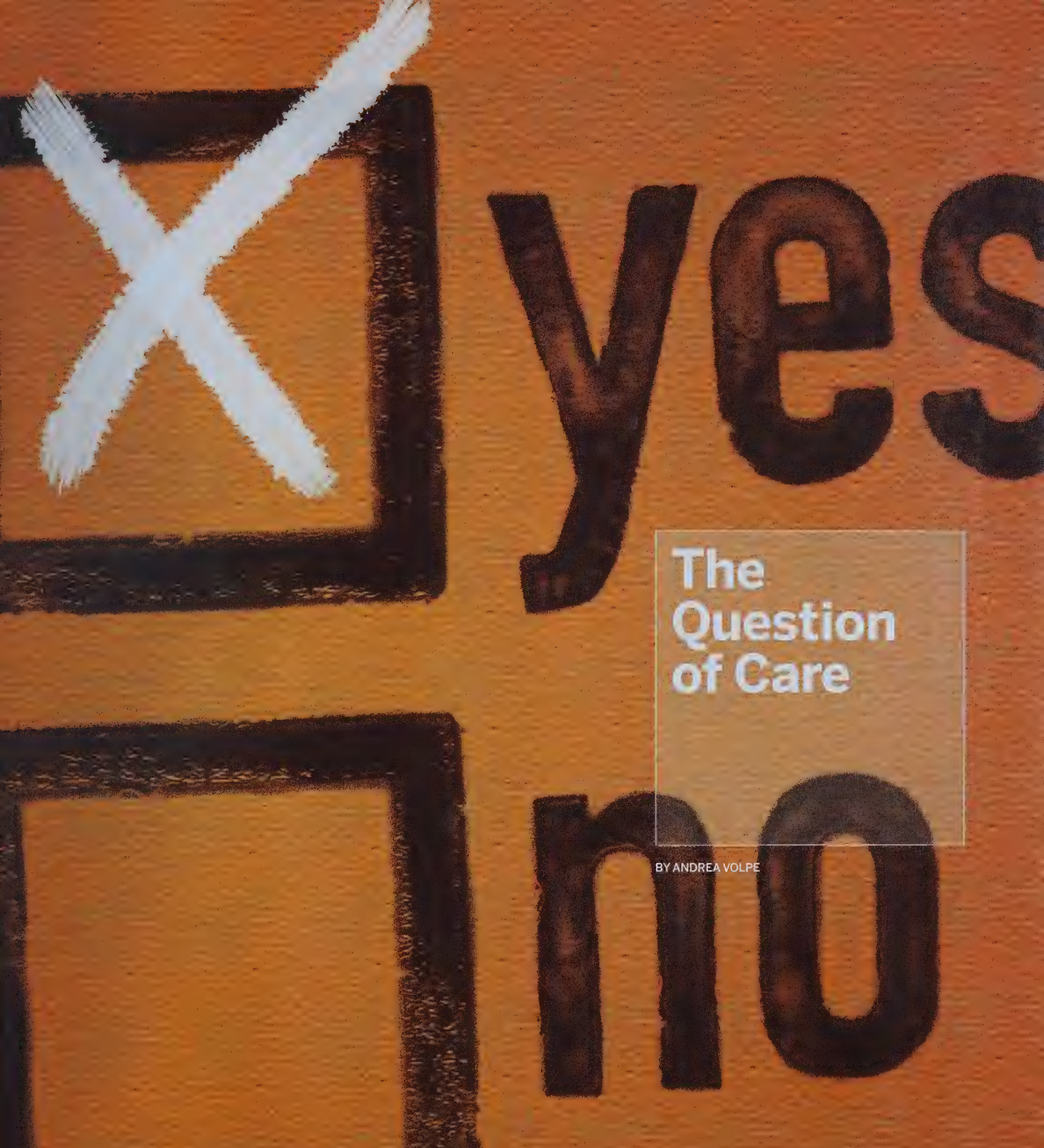
“One way to let humans play to their strengths,” says Obermeyer, “is to let computers help us process some of that information and turn it into more precise probability predictions.” Obermeyer, who is an acting associate professor of health policy and management at the University of California-Berkeley’s School of Public Health and a researcher in the Department of Emergency Medicine at Brigham and Women’s Hospital, adds that “a doctor’s job is to take in and process a ton of information and turn it into a probability judgment—about the likelihood of a disease or the likelihood that a potential treatment will benefit the patient. A lot of what we do in routine medical care is solve problems that computers are really good at solving.”

That’s where machine learning comes in—the tool kit of algorithms and statistical techniques that, combined with twenty-first century computing power, can analyze the immense amounts of data produced while caring for patients. These computational tools have the potential to transform how doctors use data to make clinical decisions for their patients and are increasingly empowering precision medicine and personalized care. Machine learning, and the big data sets it requires, is transforming how physicians approach patient care and clinical and translational research.

The soul of the machine

In a now-famous paper published in 1950, British mathematician and logician Alan Turing asked, “Can machines think?” His question planted the seed of an idea: artificial intelligence. The 1940s and 1950s saw the development of artificial neural network algorithms, which were modeled on the way the brain’s neurons respond iteratively to stimuli and which are the origins of today’s deep learning and artificial intelligence applications and expert systems.

MATTIAS PALUDI



The Question of Care

BY ANDREA VOLPE


John Halamka

When it comes to AI applications in health care, the spark, says John Halamka, the International Healthcare Innovation Professor of Emergency Medicine at HMS and chief information officer at Beth Israel Deaconess Medical Center, came from the Obama administration, when, in the 2009 American Recovery and Reinvestment Act, it provided incentives to encourage the adoption of electronic health records.

Among the first clinical decision-support tools were paper flowcharts and checklists; these capacities are now built into EHRs to help intelligently filter information. Real-time electronic alerts and reminders help ensure preventive care such as cancer screenings and management of chronic diseases such as diabetes. They can also provide guidance to physicians on drug selection, dosage decisions, drug-interaction screens, and disease-specific orders that reflect best practices. Machine learning can also improve health care delivery. Beth Israel Deaconess, for instance, uses machine learning to predict operating-room time needed for each patient and to flag patients who are unlikely to show up for appointments.

One of the obstacles to capitalizing on the potential of EHRs has been their proprietary formats. That's changing, however, thanks to Fast Healthcare Interoperability Resources, a tool that is helping developers more easily create apps and tools from EHR data. Mobility also matters: the online SMART App Gallery of software includes patient- and clinician-facing apps that allow for data sharing among patients and provide clinicians with app-based diagnostic tools.

Mining resources

Unlocking the potential of EHR-based big data for clinical research depends on machine learning, the algorithmic and statistical tools that excel at identifying patterns and applying a learned pattern to new data in order to make predictions. Because these algorithms are designed to solve these kinds of problems, they make what Obermeyer calls "good thinking partners" for doctors.

In the mid-1980s, when Isaac Kohane, the School's Marion V. Nelson Professor of Biomedical Informatics and chair of the Department of Biomedical Informatics in the Blavatnik Institute at HMS, interrupted medical school to pursue a doctorate in computer science, medicine, he says, "was already so overwhelmed with information that it was becoming challenging to turn facts into knowledge." Although the tools of artificial intelligence promised a way to learn from patients, there first needed to be a data infrastructure to work from. Kohane and colleagues wondered whether de-identified, privacy-protected clinical data from EHRs could be combined with genomic data to form a single database capable of providing the large data sets needed to advance research on genetic diseases.

This need led to Informatics for Integrating Biology and the Bedside, or i2b2, a research platform for mining EHR data. i2b2 was first funded by the National Institutes of Health in 2004, with Kohane as the project's principal investigator. Released in 2007, the software behind i2b2 allows for information held in clinical records systems to be combined with genomic data in a secure HIPAA-compliant database. The platform is free, scalable, and shareable, and now widely used at NIH's Clinical and Translational Science Award sites.

The platform is also a promising precision-medicine tool. Consider pharmacogenetics, a field that investigates the genetic basis of a patient's response to drugs. Many drug protocols for diseases from cancer to diabetes have been one size fits all. Yet, says Kohane, with access to large sets of genomic data as well as data on patients' responsiveness to drug treatments, clinicians can "rationalize picking the right drug for you." The tool will also enable researchers to develop clinical trials of drug protocols based on a patient's genetics and the genetic variants of their disease. This, in turn, will lead to genetically informed, trial-tested personalized drug treatments.

The spark was the 2009 American Recovery and Reinvestment Act, which provided incentives to encourage the adoption of electronic health records.

Today, EHR-driven genomic research is a field of its own. But it's taken new tools to extract information from EHRs because they include many different types of information. That's where natural language processing, a subset of machine learning that uses algorithms to turn text into data, comes in. Researchers are using such algorithms to more accurately identify patients with the phenotypes they hope to study. Better data are driving discovery.

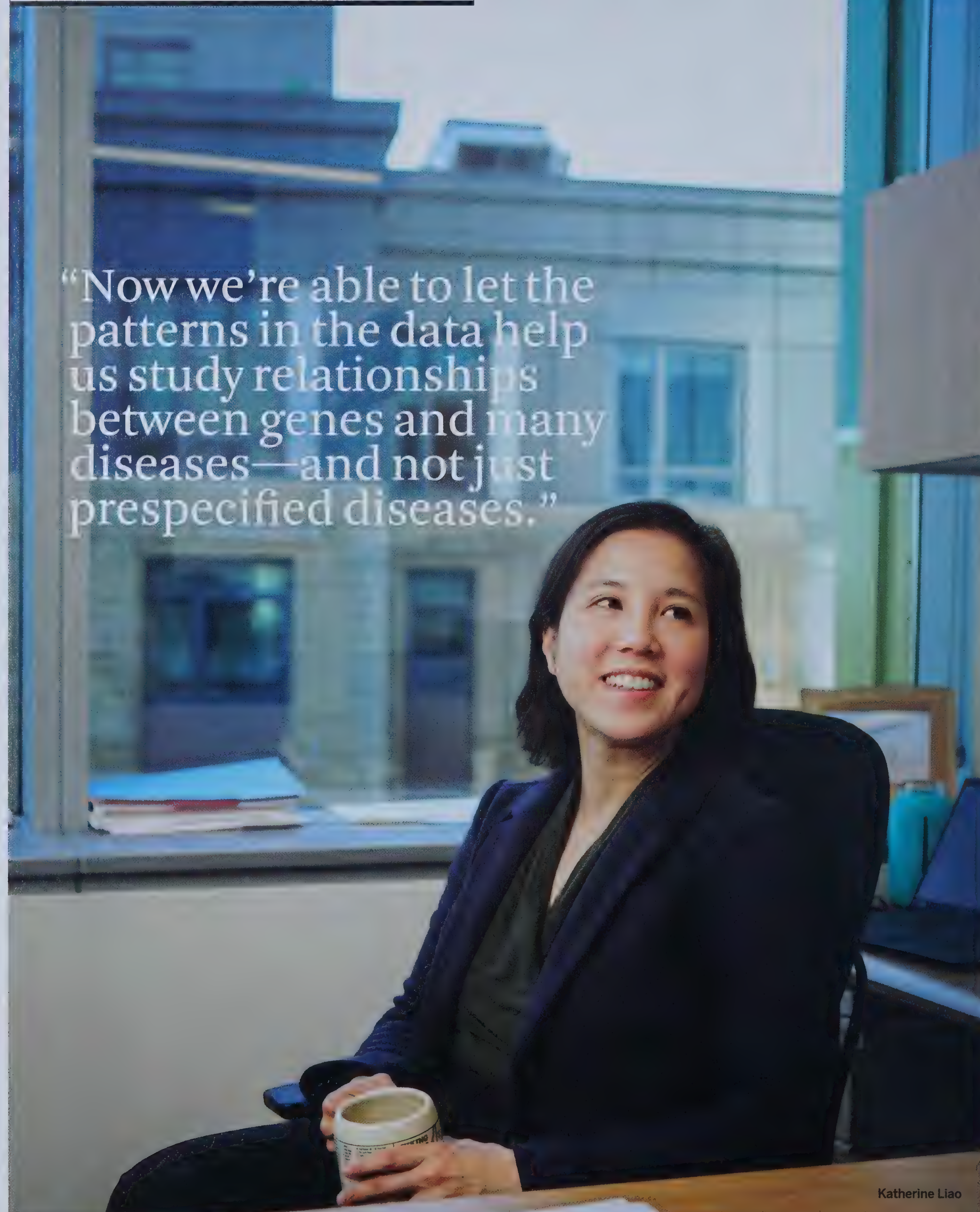
Building better care

When it comes to research, says Katherine Liao, "I always start with patients. My questions come from the unanswered questions that come up all the time as part of clinical care." Liao, an HMS assistant professor of biomedical informatics and an assistant professor of medicine at Brigham and Women's Hospital, began thinking about the "kinds of questions that could be asked of EHR data that we probably couldn't ask before" while a rheumatology fellow at the hospital and involved in the i2b2 project.

Liao's clinical practice and research focus on rheumatoid arthritis, an autoimmune disease in which the immune system attacks the lining of joints, causing inflammation and damage to the surrounding cartilage and bone. Recently, studies have found that other

"Machine learning is not about replacing clinicians; it is about enabling clinicians to practice at the top of their license."

JOHN SOARES



Katherine Liao

JOHN SOARES

tissues and body organs can also be affected by the inflammation. When diagnosing the disease, physicians use a patient's medical history, physical exam, and diagnostic tests.

Liao's research questions focus on genetic risk factors for the disease, factors that could allow for earlier diagnosis, better disease management, and better treatment decisions. Although rheumatoid arthritis is the most common inflammatory autoimmune joint disease, it is relatively uncommon statistically, affecting just 1 percent of the population worldwide. Such a small patient population means that it can be hard to fill studies with enough people to conduct robust studies.

As part of the i2b2 project, Liao and her team wanted to tap EHR data but first needed to devise an approach that would accurately identify patients with rheumatoid arthritis. She and her colleagues found that machine learning could help them design a highly accurate classification algorithm using coded data from EHRs along with data extracted from narrative clinical notes using natural language processing. After running the algorithm, they had a data set of 4,500 patients and they had it in 18 months rather than in the decades such recruitment would usually take. Even better: the same algorithm worked just as accurately on EHR data from other institutions.

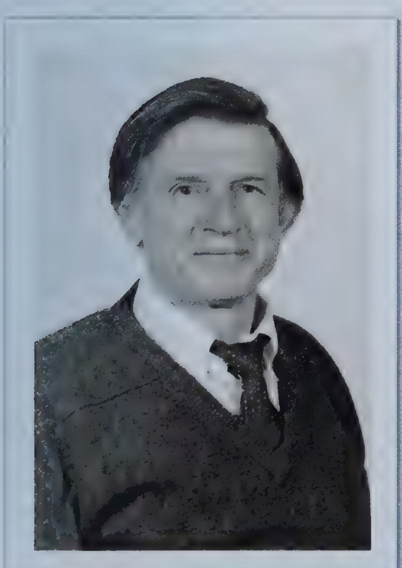
Machine learning, coupled with the ability to more fully mine EHR data, has changed the way researchers approach studies. Prospective cohort studies have traditionally been designed to investigate specific outcomes and test specific hypotheses; researchers need to decide ahead of time what data they want to collect. Since 1948, the Framingham Heart Study, for example, has been used to elucidate the causes of heart disease. Patients have been followed for years with periodic interviews used to gather information on behaviors and how they influence heart disease. In such studies, says Liao, "questions or topic areas that were not considered at the outset can prove difficult to study because the appropriate data would not be available to analyze."

By contrast, in research driven by EHR data and machine learning, algorithms can analyze health and genomic data and identify meaningful patterns previously unknown to researchers and clinicians. "Now we're able to let the patterns in the data help us study relationships between genes and many diseases—and not just prespecified diseases," Liao says.

Studying EHR data has informed Liao's clinical practice, including how and when she screens patients for lipids, her choice of treatments, and how she addresses the topic of genetic risks with patients. These days, Liao and her team are studying whether they can develop algorithms "that can tell us, in real time, what is the probability of having or developing a certain condition or an unwanted outcome." Such real-time analysis would transform prevention and early diagnosis efforts, including informing how doctors manage conditions such as rheumatoid arthritis in clinical settings.

Everything old

The future of data-driven medicine will focus on prediction and personalization. "Machine learning," Halamka says, "is not about replacing clinicians; it is about enabling clinicians to practice at the top of their license, delivering the right care in the right setting." Clinical care is also becoming more participatory and patient-centered, easing the flow of doctor-patient information.



In 1964, G. Octo Barnett (left), MD '56, founded the Laboratory of Computer Science at Massachusetts General Hospital. One of the lab's goals was to develop a programming language applicable to medicine. From that idea came MUMPS, a programming language that helped usher in electronic medical records and clinical systems.

Liao and her team are studying whether they can develop algorithms that can tell us what is the probability of having or developing a certain condition or an unwanted outcome.

Halamka says that the EHR is already getting smarter as medical care is increasingly mobile, interactive, and participatory. Patients at Beth Israel Deaconess are using BIDMC@home, a mobile app that allows them to send health data to their EHR, making them more active partners in providing the data that doctors can use to improve their care, especially for chronic conditions. A sense of what's on the clinical care horizon can be found in a few of the projects underway in the hospital's Health Technology Exploration Center: health care features incorporated into common household appliances, apps to help manage anxiety and depression, and telemedicine apps to provide specialty care globally.

Sharing data is as important as the tools used to analyze it. Several of Kohane's current projects rely on data sharing to help solve otherwise intractable problems. The Undiagnosed Diseases Network distributes data among twelve centers to help diagnose and treat rare, undiagnosed genetic diseases. Kohane's Network of Enigmatic Exceptional Responders Study investigates the genetics and immunology behind why some patients have a much better than average response to drug treatment. Together with Paul Avillach, an assistant professor in biomedical informatics, Kohane is developing a patient-centered data commons that will allow patients options on how they share their health data.

For Obermeyer, the power of machine learning lies in its capacity for making health policy smarter and informing decisions on how to manage care for high-risk patients. "If we look at our health care system," he says, "It's clear we're not making great decisions. Algorithms can help."

Paradoxically, new computational tools, and the data-driven infrastructures they draw from, are leading physicians back to what Kohane calls "small data"—and the fine art of listening to patients.

"I give much more weight to what patients tell me in all those small conversations," he says.

With the rise of tools that transform the notes from doctor-patient conversations into data, two of the physician's oldest clinical tools—listening and note-taking—are well on their way to becoming medicine's newest tools for discovery. HM

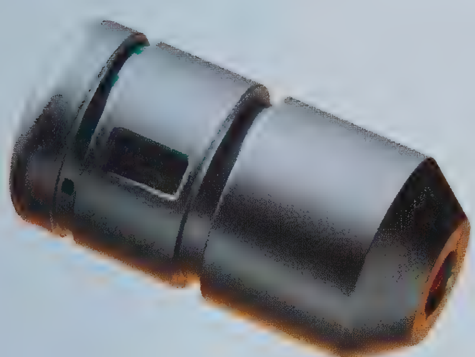
Andrea Volpe is a Massachusetts-based writer.

From the "teledactyl" device in *Science and Invention* in the 1920s to the medical tricorder in *Star Trek: The Next Generation* in the 1980s, science fiction has posited ways in which medical data would be captured and communicated.

The integration of artificial intelligence into telemedicine is enhancing the delivery of rural care and the training of specialists

To Boldly Go—Remote

BY SCOTT EDWARDS



The history of telemedicine—providing patient care from a distance using telecommunications technology—dates, somewhat surprisingly, to ancient times, when the Greeks and Romans used smoke signals and beacons to warn neighboring villages of disease outbreaks or to announce births and deaths.

With the development of radio and television, speculative articles on telemedicine bloomed. In the mid-1920s, a magazine called *Science and Invention* posited the notion that doctors would, in the future, use television and microphones and tend to patients via a "teledactyl" device, a tool with articulated appendages that would respond to remote manipulation by the physician, allowing the doctor to "feel his patient, as it were, at a distance."

From these humble yet futuristic beginnings, telemedicine today is on the brink of another revolution: the use of artificial intelligence, made possible with computers, algorithms, and technology, to analyze vast amounts of medical data to provide physicians and other caregivers with treatment guidance and recommendations, often remotely.

Service upgrade

The advent of the World Wide Web in the early 1990s brought about an information explosion that made possible the remote transfer of vast amounts of data, from basic vital signs and patient medical records to images from x-rays and MRIs among and between points of care. This virtual sharing capability has ushered in a new era in which people can use wearable devices to monitor personal health data and medical professionals can employ machine learning, pattern recognition, and computer algorithms—the basic elements of artificial intelligence—to diagnose, treat, and manage patients in clinics, hospitals, and at remote sites throughout the world.

"The marriage between a physician and artificial intelligence provides an opportunity for substantial growth," says Paolo Silva, an HMS assistant professor of ophthalmology and the assistant chief of telemedicine at Joslin Diabetes Center's Beetham Eye Institute. "By 'training' artificial intelligence with different skill sets, it can potentially lead to new medical discoveries."

"Modern AI techniques can really affect the flow of decision-making information," says Douglas Perrin, an HMS instructor in surgery and senior scientist at Boston Children's Hospital who has spent the past fifteen years translating research advances in computer science into medicine. "It's another tool in the physician's tool kit."

HMS physician-scientists are making inroads in using AI-based systems for teleimaging and remote surgical education, training, and practice. Such initiatives could play a role in the future of how medicine is practiced remotely. And these systems may help fill a growing gap in health care, especially in rural and other underserved areas.

According to a 2016 report from the U.S. Centers for Disease Control and Prevention, data gathered between 1993 and 2015 indicate that nearly 20 percent of U.S. adults do not have regular access to health care. The National Rural Health Association reports that, as of October 2018, more than 120 rural hospitals have closed since 2005. Overall, the association says, more than one-third of rural hospitals are vulnerable, a number that jeopardizes access for an estimated 11.7 million patients.

In addition to the falling numbers of health care facilities, rural hospitals and clinics often do not have access to the array of specialists available in the more populated areas of the country. The use of AI may help reduce this dearth of rural specialists, according to a recent *Forbes* article on democratizing health care, by allowing specialists to remotely access a wealth of patient data and consult with local physicians on diagnosis and treatment determinations.

Pixelated care

At Joslin, Silva focuses his work in ocular telehealth for diabetic retinopathy, a condi-

tion that results when high blood-sugar levels damage the tiny blood vessels that supply the retina. At its most severe, it causes the retina to detach and leads to permanent vision loss.

Silva also directs telemedicine and retinal imaging research programs. One such program has led to collaborative efforts in the Philippines with Joslin and the federally funded Diabetes Retinopathy Research Network.

Based on this research, Silva has collaborated on the development of a fully automated computer algorithm to detect hemorrhages and microaneurysms, hallmarks of diabetic retinopathy, using ultrawide-field imaging. Unlike standard retinal imaging, ultrawide-field imaging captures up to 82 percent of the retinal surface in a single image, enabling clinicians to detect lesions on the retinal periphery.

Says Silva, "Our data show that when microaneurysms occur predominantly outside the fields that are imaged with traditional fundus photography, the eye is at high risk of worsening, increasing the risk of diabetic retinopathy progression over the long term." Fundus photography captures the interior surface of the eye, including the retina.

In April 2018, the U.S. Food and Drug Administration approved the first medical device that uses artificial intelligence to detect greater than a mild level of diabetic retinopathy. In mild diabetic retinopathy, the retinal blood vessels weaken and, in small areas, balloon to form microaneurysms. Silva says this device uses traditional narrow-field fundus photography rather than ultrawide-field imaging.

Silva's pilot study, presented in part at the 2014 annual meeting of the Association for Research in Vision and Ophthalmology, included 2,000 retinal images. To confirm the findings in a larger cohort of patients, he has since expanded the study to include more than 200,000 images. If successful, this algorithm may be able to identify lesions undetected by ophthalmologists, help clinicians predict the progression of the condition, and allow for the fine tuning of treatment plans. The need for such a tool is considerable.

In this country, nearly 4.2 million people have some form of diabetic retinopathy, according to the CDC, with more than 650,000 people at risk of losing their vision.

Part of Silva's telemedicine practice at Joslin includes work within this vulnerable population. Through the Joslin Vision Network, created by Lloyd M. Aiello, a former HMS professor of ophthalmology, Joslin ophthalmologists are connected to more than ninety sites in twenty states. Many of the sites are within communities served by the Indian Health Service and the U.S. Departments of Defense and Veterans Affairs.

JOHN SOARES (SPREAD)

Hashimoto's efforts involve virtual reality technology that trains surgeons on the safe, effective use of surgical instruments.

Through the program, Native Americans, a population with the greatest risk for diabetic retinopathy, can have retinal images taken annually. This effort has generated some 20,000 images. These are sent to the network's reading and evaluation center in Boston, where clinical experts in diabetes eye care evaluate them for diabetic retinopathy and other ocular pathologies. Although the network doesn't use specific AI applications, Silva hopes to apply his research with the Diabetes Retinopathy Research Network and "leverage artificial intelligence technology to provide care by reading retinal images at the point of care and decreasing the burden of evaluating images."

Operating at a distance

As the surgical artificial intelligence and innovation fellow at Massachusetts General Hospital, Daniel Hashimoto spends much of his time investigating ways to improve the efficiency and quality of technical skills acquisition among surgeons. He also researches ways to integrate artificial intelligence into telemedicine in surgery. His work has been focused on the development of algorithms that can analyze video of surgeons conducting laparoscopic cholecystectomies, laparoscopic sleeve gastrectomies, and per oral endoscopic myotomies for ways to improve the safety and efficiency of their surgeries. In addition, through a process called telementoring, Hashimoto, who also is an HMS clinical fellow in surgery, has researched virtual and augmented reality platforms to remotely train surgeons.

Hashimoto is collaborating with scientists at the Computer Science and Artificial Intelligence Laboratory at MIT to analyze the millions of pixels in each of the twenty to thirty frames per second that are captured in videos of surgeries and create prediction models to help improve surgical procedures. Drawing on a library of data contained in videos that the researchers collected during the past four years from collaborating institutions, publicly available sources, and other databases, the algorithms the team has developed can predict the outcomes of techniques being used by the surgeons and, in turn, be used to guide them on ways to improve.

"Our hypothesis is that there is a sequence of events that can happen in an operation," says Hashimoto. "Our work is focused on how we can use the data gleaned from the videos and make them actionable to help surgeons perform safer procedures for patients."

Hashimoto's efforts to remotely mentor surgeons as they acquire new skills involve virtual reality technology that trains them on the safe, effective use of surgical instruments. This virtual reality environment relies on algorithms to capture a variety of metrics, for example, how many millimeters the surgeon is moving an instrument or how many degrees they are rotating their wrist.

The effectiveness of this training approach has shown results; participating surgeons have improved their technical skills and have needed fewer hours to achieve proficiency benchmarks such as those set by the American Board of Surgery's Flexible Endoscopy Curriculum. A study published in March in the journal *Surgical Endoscopy* by Hashimoto and his colleagues indicates that the team's proficiency-based curriculum increased surgeons' first-time pass rate for the Fundamentals of Endoscopic Surgery exam from 80 percent to 100 percent.

Silva, Hashimoto, and others are making advances in applying artificial intelligence to telemedicine and, they hope, to improving patient care in clinics far and near. HM

Scott Edwards is a Massachusetts-based science writer.

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DO NOT WRITE BELOW THIS LINE

in 5

A conversation with Marcia Haigis, HMS professor of cell biology, Department of Cell Biology in the Blavatnik Institute at HMS

Why do you study the function, and malfunction, of mitochondria?

We have long known that mitochondria are the engines of the cell, but I love thinking about the role of mitochondria beyond the classical ATP-producing powerhouse. They have so many functions: cell growth and cell proliferation, cellular detoxification, oxidative-stress damage control, and intracellular alert to stress, damage, or fuel and energy excess. Mitochondria are true rheostat sensors.

Our lab is particularly interested in the molecular machinery that allows mitochondria to help cells deal with stress; we want to understand how the enzymes that enable this function are regulated. Understanding how these regulatory pathways contribute to mitochondrial function and dysfunction will have profound implications for understanding conditions ranging from diabetes and obesity to cancer and aging.

Who inspires you?

My lab team inspires me. Every day. My students, my postdocs, they have so much energy and creativity. I am inspired when they come to me with out-of-the-box questions. I find it especially inspiring when we work as a team. We are stronger when we feed off each other's ideas, enthusiasm, and creativity to arrive at new solutions. I'm also inspired when I see trainees arrive at their own eureka moments and build their own power and confidence.

What is your road not taken?

I was always curious about biology. Growing up, I was taught that if you like science, you go to medical school. So that's what I prepared for. As a freshman, I worked as an EMT in the ambulance corps. To fulfill my hours, I took overnight shifts. One morning, I was walking back to my dorm, bleary-eyed, and took a shortcut through the biochemistry building at the University of New Hampshire. On the walls were tons of scientific posters by students and postdocs. At that early morning hour, there was only one open door and only one person in the office: biochemist Richard Cote. I asked him if he could tell me a little bit about the posters. My question turned into a two-hour conversation—and a job offer. I ended up working in his lab for three years and, as an undergrad, publishing my first first-author paper.

What has been your greatest a-ha moment as a scientist?

That shortcut through the biochemistry building. Learning about basic research that morning was one of my more memorable such moments—the realization that you could actually make a career out of solving puzzles, out of curiosity, out of exploration and fun. That first summer, I realized that answering questions and solving scientific puzzles just felt right.

What do you see as the single biggest challenge or greatest opportunity scientists face today?

Today, scientists have the opportunity—and the responsibility—to be advocates for science, education, and mentorship; for health care and science communication; and for diversity. We should really do what we can to feed the discovery pipeline but also communicate with members of the public, so they can understand the importance of science and appreciate the effect it has on their lives.

—Ekaterina Pesheva

Galina Gheihman (left) wrote the essay being featured in this issue of *Harvard Medicine* while a student in the Mentored Clinical Casebook Project, an HMS course. For the course, Gheihman was paired with a clinical mentor and a patient. Gheihman closely followed her patient for one year, recorded their interactions, and researched the cultural, scientific, and socioeconomic factors that may have affected her patient's medical condition.

JOHN SOARES

revelations

On the road to becoming a doctor, a medical student learns she must first deeply know herself by Galina Gheihman

They say doctors are natural storytellers. Perhaps they are not so much storytellers themselves as the conduits by which patients' stories reach a larger audience. Doctors rarely need to work hard to find stories: patients seek their help and tell their stories themselves.

So why do I find it so difficult to write this story? Why is it such a struggle to get the words out onto the page, to bring my fingers to the keyboard and spell out what I have seen, heard, felt?

Perhaps because I simply could not capture the infinite minuteness of the details I have observed. And not just the millions of pieces that form the scenes I observed and the sounds I heard, but also how all of this was multiplied and amplified and reflected in the feelings, thoughts, and insights that fluttered about me and within me as they happened.

I did not know how this journey would change me. Writing has allowed me to slow my thoughts down, to record how they progressed and changed. Reflection, if we allow it to, will often take us into a new place that we may not have intended to go.

Laura was a relatively healthy young woman when she experienced her first grand mal seizure. It started off inconspicuously enough. She and her husband, Matt, turned in for an early night with no expectations that anything was amiss. Matt awoke to her thrashing in the bed beside him and their dog, Bella, running around the bed and barking up a storm. He rushed to turn on the lights, revealing a frightening scene. Laura's body was convulsing; her eyes were open but rolled back. He called 911 for an ambulance. A few minutes later the seizure was over, and Laura awoke.

Reflecting on the experience some time later, Matt recalled that Laura had the classic signs of a major epileptic seizure: tonic-clonic contractions, eyes rolled back, foaming at the mouth.

Laura does not recall this story, of course. She was unconscious for most of the time; if she was not entirely unconscious, then at least she was not capable of remembering the experience or interacting with others during the seizure.

Fortunately, she responded very well to medications and has not experienced any grand mal seizures since. She reports no side effects from the medications but feels "forgetful and needs to make lists," although she is still able to focus and function in her work.

Once Laura had the diagnosis of epilepsy, she realized there may have been warning signs in the preceding years. Three or four years before her seizure, she began to experience an auditory hallucination, what would later be called her aura—a type of seizure activity that occurs locally in the brain and often presents as a visual or auditory hallucination.

Her aura was the sound of a man talking, a particular man with a deep, smooth voice that would come and go, at first loud and then softening. This occurred rarely at first, but soon began to increase in frequency. She was not particularly bothered by the hallucination itself, but she was always aware of it occurring. It would often signal the onset of a headache. As the voice became louder and stronger, she became concerned and visited her primary care provider, who attributed the voice to stress and prescribed a sedative and an antidepressant to lift her mood.

Laura was taken aback by these suggestions and had absolutely no intention of going on antidepressants or of taking strong sedatives. Disappointed that she had been dismissed and did not have an answer to this concerning problem, she tried her best to simply ignore the voice and not allow it to get her down.

While she told her husband about the symptoms, she felt embarrassed and concerned; her grandmother on her father's side had been hospitalized for mental illness. She feared that she, too, might be experiencing the first signs of mental illness. She was, in fact, relieved when she was diagnosed with epilepsy and her auditory auras were explained. I would later learn that the auditory hallucinations fit her eventual diagnosis of left temporal lobe epilepsy, the most common form of adult-onset epilepsy and the one most closely tied to auditory hallucinations; the area causing the seizures is located in the auditory center of the temporal lobe in the brain.

Since beginning medication, Laura considers herself to be under excellent control. She is currently on the newest anti-epileptic drug, which is also the safest one for women of childbearing age.

When I met my mentor, Dr. Bertill, I learned that she had developed a practice in which she managed women with epilepsy who were either pregnant or in the prime of their reproductive years and interested in becoming pregnant.

New drugs are becoming available, and new formulations, developed to minimize side effects and help regulate and suppress seizures. Important for the population of female patients of childbearing age, the new medications are less apt to cause birth defects than those available previously, meaning that women with epilepsy now have the opportunity to have children in a way that would be safe both for them and for the developing fetus.

Dr. Bertill was determined to make it possible for her female patients to start a family and live as normal a life as possible. As a clinician-scientist, she knows how to pose the right scientific questions by identifying gaps and questions that arise within her own practice. In turn, she also can provide patients with the latest evidence and information about their choices and the associated risks for their individual condition and circumstances.

According to Dr. Bertill, those who have epilepsy and manage it well are not proud to disclose it; they fear discrimination.

When it comes to pregnancy, these concerns are even greater, but Dr. Bertill does not see managing a pregnancy with epilepsy any differently than managing one with diabetes or hypertension. In all cases, these patients require medications and doctors need to strike a balance between managing the benefits of the medications, and the risks to achieving the best possible outcomes for both mom and baby.

Laura went in to see Dr. Bertill primarily to get the okay to start trying to conceive. She was already on the safest medications in terms of pregnancy and risk for major congenital malformations, so there was no need to adjust them. However, Dr. Bertill did describe how the dosages of these medications might need to increase during pregnancy. The treatment of epilepsy during pregnancy is a balancing act.

Laura found out she was pregnant on Christmas Eve and called me two days later. She had not been anticipating a positive test. She and Matt did not quite know what to do with the information.

I was honored that she decided to call me and that she felt comfortable enough to share this information. It was a new role for me.

One thing that I kept running up against over the course of this experience was that of the "third space," the potential space or

distance that exists between the world of our patients—their beliefs, stories, ideas, and homes—and the world of medicine—clinical appointments, observations, and our mentors. Between these two is an uncertain, often amorphous, and constantly changing, space that we, the medical students, occupy.

Living in the third space offered certain benefits and privileged access to both the world of my patient and the world of medicine. It offered the first step into our patients' lives, and I would leverage the "clinical connection" to ask some difficult questions. But at other times I felt that I was perhaps trespassing beyond the limits of my third space and encroaching onto property that was the patient's own. All this just as I was starting to grow into my white coat.

As physicians we gain deep access to many aspects of our patients' lives, and yet, in the end, we must recognize that we are only observers and can never be as closely involved as we may want to be.

I felt lucky to be included in Laura's initial visit to the OB/GYN office where she would have a first ultrasound for the baby and meet her physicians. Because Laura was considered a high-risk mother, given her history of epilepsy and her advanced maternal age, the ultrasound was done at seven weeks rather than the usual time of between ten and thirteen weeks. It was surprising to me that we were able to see the fetus at all when, as the ultrasound technician estimated for us, it was only about the size of a blueberry.

For me, the most amazing part was being able to see the little flutter of the fetal heartbeat. I say flutter because it truly looked like a tiny butterfly, no more than a few millimeters across, that opened and closed its little wings, unfurling them at a remarkably quick pace. I've heard that hummingbirds can flick their wings as fast as 40 times a second or so, and I was reminded of this remarkable fluttering as I looked on. The baby's heartbeat measured 140 beats per minute. Perfectly healthy.

Thinking back on that tiny fetal heartbeat makes me think of the numerous times I have listened to my father's heart. When I was younger, I loved curling up next to him as he sat on the armchair reading or on the sofa watching television. I would press my ear against his chest and focus all my attention on the regular *thump-thump*, *thump-thump* of his heart.

JOHN SOARES

"Thinking back on that tiny fetal heartbeat makes me think of the times I have listened to my father's heart. I would press my ear against his chest and focus all my attention on the regular *thump-thump*, *thump-thump*."

On one of these occasions, I had a significant realization that would somehow affect how I viewed hearts in the future. I realized that his heart and my heart and all the hearts in all the people around me had been beating nonstop since the very first day they came into existence. This was a grand and unparalleled realization, and I remember being not only awed by the truth of this fact but also by the sheer force of the expansive, fleeting wonder I felt.

Seeing the baby's heartbeat took me back to that moment of wonder. Only seven weeks and already that little heart was pumping away, regular and autonomic.

Of all the classes I took this year, Medical Ethics and Professionalism provided the most insight and relevance to my clinical experience.

Our topic for one of these classes was abortion. We were due to discuss the moral arguments for and against this controversial practice and, in preparation, we had readings and a short essay response to complete. I was curious to learn what the major arguments on each side were and to read true and logical accounts of these arguments.

As part of the class, we filled out an anonymous survey. Among numerous questions highlighting particular scenarios and options, I remember being asked, How many people do you personally know who have had an abortion? I answered zero, reflecting on how interesting it was that I had comfortably come to conclusions about this topic and about my own feelings and beliefs on it without ever having had to face it in real life. I had not known anyone who had considered or even followed through with this option.

Here is an excerpt from my assignment for that class:

In sum, the rights of all patients—pregnant or not—to bodily integrity and informed consent must be respected, "regardless of the impact of that person's choices on others." A woman's autonomous and fully informed choice, made with the interest of both her fetus and herself in mind, should be upheld whenever it is safe to do so.

Little did I know that just a few days later I would be staring at my inbox, trying to process the shocking, completely unexpected news that Laura and Matt were considering a termination of their pregnancy after so many weeks and months of expecting.

Hi Galina,

Unfortunately, we received some pretty bad news about the baby. Last Monday the test results came back positive for Down syndrome. This has left us with an agonizing and ethical decision to make—whether or not to continue the pregnancy... We are also testing to see if this is something I can carry or that will affect any future pregnancies should Matt and I want to try for another baby down the line.

Perhaps we can meet to discuss in a few weeks. It's still quite painful to speak about and I'm barely holding it together as is. By that time our decision will be made as well and I will be, hopefully, in a much better emotional state. Sorry to delay meeting; I do want to meet, I just can't right now.

Laura

I thought this would be a story about a baby, about pregnancy, birth, new life. What I couldn't have anticipated was that it could also be a story about death. Perhaps I should have expected this, for you cannot have life without death.

It was not long after the first email from Laura that I received devastating news: Laura and Matt had decided to terminate the pregnancy. My first reaction was deep and disturbed. I was hurt, even shocked by the news, and I could only imagine what they must have been going through, how difficult their discussions must have been. It would be weeks before we spoke again.

We do learn a lot about our patients and about their medical conditions, but we would be fooling ourselves if we thought we knew everything about them.

Hi Galina,

Thank you for your kind voicemail last night. I was on the other line with my mom talking about everything. Matt and I have decided to end the pregnancy so I'm in the middle of trying to make the arrangements to do so, as well as securing some counseling/therapy for us. I'll be in touch over the next few weeks. Thank you for keeping us in your thoughts.

Laura

After receiving the news, I walked around stunned, not knowing how to feel or how to react to the situation. I was strongly affected, but what was I feeling? I could not say. I struggled to understand, and I was afraid at first to ask for help. I was not yet ready to speak. It took a while for me to realize that what I was experiencing was grief and that what I was dealing with was, in essence, my first death.

In the moments after learning about Laura's results, one of the strongest feelings I had was a real sense of mourning. It was a loss after all, and I could not help but wonder how Laura and Matt were feeling. The termination aborted not only the child but the dreams, feelings, hopes, and experiences it represented and engendered.

I spent almost two weeks in silence trying to process and understand my emotions. I decided to speak first with my father, whom I have often used as a guide and a mentor when faced with circumstances that challenge me to think in new ways. I phoned him and asked him whether he would be willing to listen, not necessarily to advise me or answer my questions but simply provide me an avenue to get my thoughts out and help me analyze them.

My father reminded me that people will make many different choices. As a physician you don't need to decide for all the people. They are your patients. They are not breaking the law. Your responsibility is to support them, without passing your own judgments.

My father has an analogy that he often uses to describe emotions when he's advising my sister or me. He says that emotions are like a wave and one must learn to surf on them. Our consciousness is only the surface and below that is a much deeper, more complex subconscious. Sometimes, if the emotion hits us just at the right time and place—and we are ready for it—we may even stand up and surf along. It's these moments where the emotion can truly drive us and take us somewhere new, further than we have ever been or we ever thought we could go.

I worried at the time about falling to pieces and knew that what I needed was not someone who could discuss the ethics or practices or technicalities of a procedure but just someone who could provide support to me. Without realizing it, this was my introduction to a key component of my professional duty as a physician: balancing one's own emotions and opinions against the needs, thoughts, and feelings of our patients.

It is all too easy to default to one's own beliefs, but the trick to becoming an open, caring clinician is to be able to solicit and support your patients' needs at the time of their care, rather than your own. This is not to say that you cannot have feelings in response to a patient's situation. Our role is to learn to manage our emotions so that we can instead focus on the patient. I should emphasize that managing does not mean ignoring or putting them aside. In fact, it takes real skill, focus, attention, and even mindfulness to be able to tune in to these emotions and get a reading on one's own body and mind; this can inform our approach to the patient.

We do learn a lot about our patients and about their medical conditions, but we would be fooling ourselves if we thought that we knew everything about them. In fact, it became exceedingly clear over the course of the year that I had gotten to know Laura much better than my mentor ever had a chance to. Dr. Bertill had seen her within the medical context, and Laura's friends and colleagues had seen her personal and social life, but where did that leave me? Straddling the third space, not quite physician, not quite friend.

Hi Galina,

Matt and I are doing much better. It's still difficult but I can now talk about it without crying, which is a huge improvement. I'm back at work as well which helps keep my mind off of things a bit. I have an appointment with Dr. Bertill coming up—are you able to attend that? If not, I can see if she can reschedule. I hope you had a good spring break and that you were able to enjoy your time off!

Laura

One of the important pieces of this experience has been developing a relationship over time with Dr. Bertill. I have to admit that when I first met her I was a bit worried about what the experience would be like and whether the two of us would hit it off or not. I was hoping to have a very warm, helpful, and incredibly dedicated mentor who would have time to teach me, explore with me, offer suggestions, and connect me with others. Instead, I found that she, too, had little idea about what we should be doing as it was her first year as a mentor with the program. The boundaries, settings, and expectations were malleable, waiting to be set by us.

What I learned from Laura is that being a patient means being vulnerable, being threatened by something from within or outside of oneself. Perhaps the greatest lesson Laura demonstrated was that being vulnerable did not mean that one was helpless or that one had to be passive.

Laura was really the first patient I met who had read about her condition on the internet. She had researched all her providers and made a choice about which physician to visit based on online recommendations and expertise. She had the confidence to seek the best care for herself and also the competence to navigate the health system and find and demand excellence. I was impressed by this and that Laura did not allow her illness to possess or overwhelm her.

Laura and Matt invited me for a visit to their home in a suburb outside of Boston on the second weekend in May.

JAKE MILLER

The Soul of a Patient, published this year, features essays from nineteen HMS students who have participated in the Mentored Clinical Casebook Project.

I brought along some chocolate for us to share and Laura had lovingly put out a mixed platter with sliced baguette, homemade green bean and avocado paste, and a fresh slice of brie she had picked up from the local grocery store. Today we would not only be sharing histories, sharing opinions, or sharing stories, we would be sharing that most fundamental of activities that bring two people closer—we would be sharing a meal.

In my last meeting with Dr. Bertill, we reflected on how this experience had been for each of us over the past year—the ups and downs of treating and spending time with Laura—and both the expected and unexpected outcomes of participating in this course.

Dr. Bertill believed that taking on a professional role was part of her responsibility to the patient. She wanted to demonstrate expertise, confidence, and competence so that the patients, too, could feel that they could rely on her as a physician, that they would have confidence in her, and feel their care was in the right hands.

It is hard to instill confidence if you are susceptible to your emotions, however. Dr. Bertill said, "When you sit with your patient, you must listen wholeheartedly, but you must also remember that you have another roomful of patients waiting for your help."

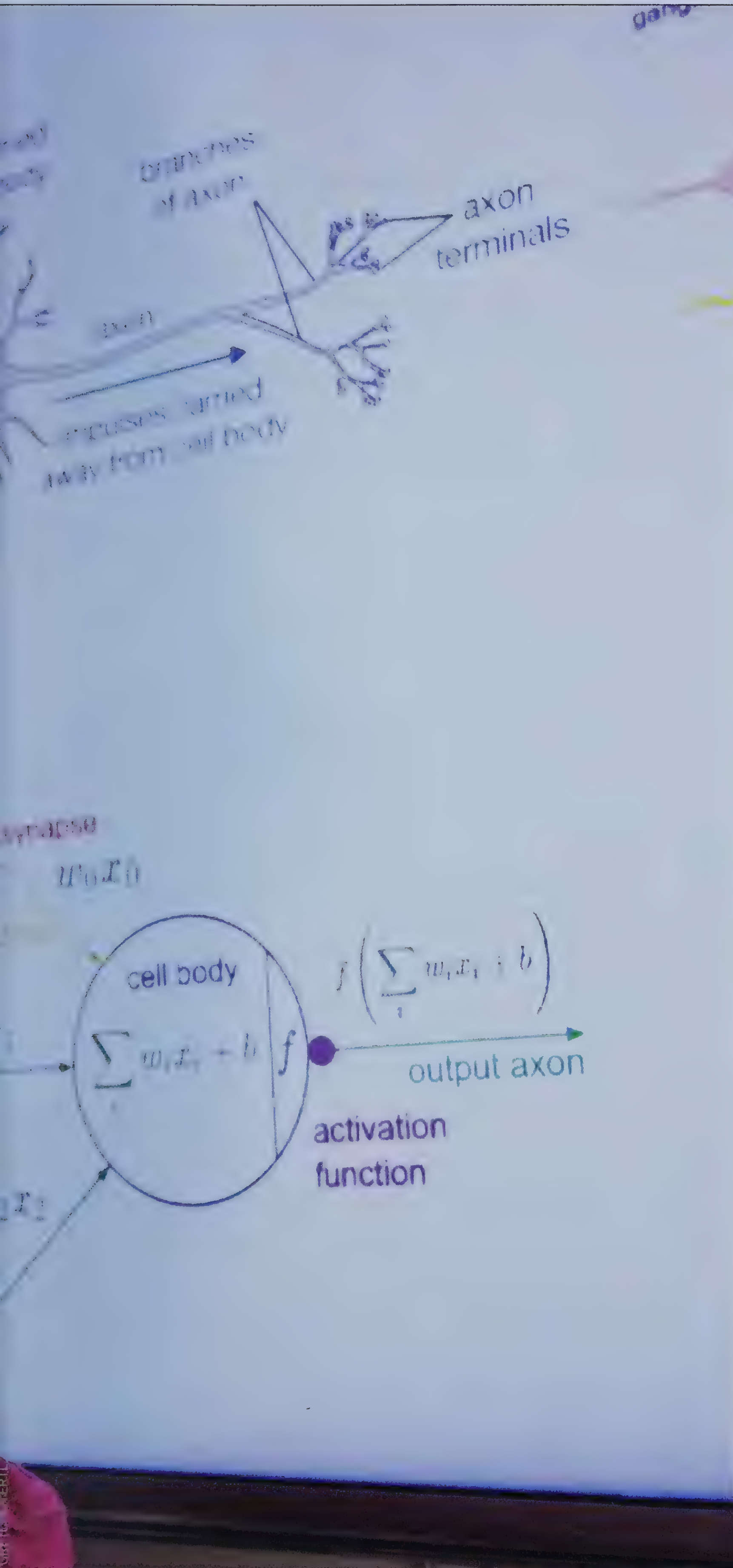
You cannot let yourself empathize so strongly with one patient who leaves you empty and incapable of helping the next one. I think the balance between sympathizing and holding my emotions back is one of the lessons that has been hardest for me and that I anticipate I will continue to struggle with throughout my training. I learned during this experience that sometimes our own emotions in a situation are unpredictable.

As we wrapped up our final meeting, I asked Dr. Bertill if she had any words of wisdom to impart. She said, "What I've learned is that every patient is so different. You cannot predict a patient's response, especially when they are faced with a difficult medical situation that is scary or concerning to them. Some of the women in my clinic come in and they are just scared and worried. Others are cool as a cucumber. But all of them are our patients, and our role is to be sensitive to their specific needs, whatever they may be."

Be sensitive, be helpful, and tend to the needs your patients express. This is both the simplest and the most difficult thing—and it is what we physicians must learn to do. HM

Galina Gheihman is a member of the MD Class of 2019 at HMS. This essay, titled "Heartbeats," appeared in The Soul of a Patient: Lessons in Healing for Harvard Medical Students, *a compilation of student essays edited by Susan E. Pories, MD; Samyukta Mullangi, MD '15; Aakash Kaushik Shah, MD '16; and Mounica Vallurupalli, MD '13. The names of the patient and the physician/mentor in the essay have been changed, and the piece has been edited for length. It appears with permission from the publisher, Gordian Knot Books/Richard Altschuler & Associates, Inc., Los Angeles, California (www.richardaltschuler.com).*


draws from biological
LGN
V1



Student Life

SAM FINLAYSON'S DESIRE to become a physician-scientist is rooted in hope and heartbreak. A fifth-year student in the Harvard/MIT MD-PhD Program who is working on his doctorate in systems biology in the Department of Biomedical Informatics in the Blavatnik Institute at HMS, Finlayson overcame severe health problems to get where he is today.

While a newborn, he contracted meningitis, which progressed to encephalitis and precipitated a years-long nightmare that included seizures, strokes, oxygen support, a surgical error that resulted in intravenous feeding, and developmental delays.

But, he says, it's not his personal health hurdles that motivate him to pursue the research he undertakes today. It's his sister, Kate, and the health problems she faced.

As a child, Kate had a brain hemorrhage that resulted in hydrocephalus. When she was in middle school, a shunt implanted in her brain to divert excess cerebrospinal fluid failed, requiring surgery that caused complications. After more than one hundred brain surgeries and years of hospitalizations, she died in 2010 at age twenty-six.

"My sister and I and our whole family have really experienced the very best and the very worst of medicine," Finlayson says. "Since early high school, I have tried to craft a career in which I could provide care to patients according to the best knowledge we have, while also nudging the boundary of our capacity a little further."

Finlayson now works in the lab of his mentor, Isaac Kohane, chair of the biomedical informatics department, and focuses on using machine learning to find treatments for rare diseases.

"We have compiled some incredible data sets measuring the effect of small-molecule drugs on gene expression in cells," says Finlayson. "I'm training large neural networks to learn the patterns in these data sets and others like them."

"The goal," he adds, "is to apply these same algorithms to data collected from hard-to-treat diseases and to identify drugs that could work against them."

Ten years ago, he and his brother created Team Hydro, a group that swims to raise money for hydrocephalus research. Since then, the team has raised more than $700,000 and sponsored ten sizable research grants. Swims across Boston Harbor have featured many of Finlayson's HMS classmates, as well as Kohane.

"The growth of Team Hydro is a testament to both the legacy of hope and perseverance that Kate left behind and the tenacity of my brother and my parents," Finlayson says.

—Randall Fox

On a **Mission**

YOU HAVE TO BE AN OPTIMIST to travel halfway around the world alone, to somewhere you've never been, and with little more than a dream. This is how Yeu-Tsu Lee found herself, in 1955, at the University of South Dakota in Vermillion, far from her home in Taiwan.

Born in Xi'an, China, in 1936, Lee began her life just before the start of the Second Sino-Japanese War. In 1949, she moved with her family to Taiwan.

"When I was very young, about five, I watched four of my siblings die," says Lee. "I am sure they would have lived if a doctor had been available. I decided then that I would be a doctor."

Although Lee had not heard of HMS before coming to the United States, once she found out it was the one medical school in this country where she could do both clinical work and research, she knew it was the place for her. She applied and, in 1957, received her acceptance—and a scholarship.

Judson Randolph, then the chief surgical resident at Boston Children's Hospital, was one of Lee's mentors. She wanted to be a surgeon and told Randolph so. He agreed that she certainly could be a surgeon, but not in Boston. Nobody would take a woman trainee.

Thus began another journey, one that took her from Boston to Ann Arbor, Michigan, and then to Columbia, Missouri, to complete her training in surgery. Eventually she became a surgical oncologist. Lee was on faculty at the University of Southern California Medical School for ten years. In 1983, she moved to Hawai'i, joined the U.S. Army Medical Corps and worked at the Tripler Army Medical Center. Hawai'i has been home ever since.

In 1991, she was deployed to northern Saudi Arabia as a U.S. Army general surgeon with the 400-bed Thirteenth Evacuation Hospital during Operations Desert Shield and Desert Storm, treating U.S. soldiers as well as Iraqi prisoners of war. She retired, as a colonel, from active duty in 1999.

Lee has served on more than fifty medical missions, in places as far-flung as Ghana, Honduras, the Philippines, and Southeast Asia. She considers herself lucky to have had the career and life she's had and cites Title IX as pivotal in leading to the parity now seen in medical schools, where half the graduates are women. It's a world far from the one she came up in, when gender was considered a handicap to career ambitions.

In fact, five decades after leaving Boston to pursue surgery, Lee journeyed back to the city, this time to accept the 2018 Dr. Mary Edwards Walker Inspiring Women in Surgery Award from her peers in the American College of Surgeons.

—Susan Karcz

Yeu-Tsu (Margaret) Lee, MD '61 | Clinical Professor of Surgery, University of Hawai'i John A. Burns School of Medicine | Tripler Army Medical Center, Chief, Surgical Oncology Section, retired

Of Pilots and Physicians, Passengers and Patients

The importance of maintaining situational awareness when the stakes—and the stress—are high

BY TAMARA FOUNTAIN

I am the daughter of an aviator. Before I could even sit up, my mom was pushing my stroller on the tarmac to visit my dad, an instructor pilot in the U.S. Air Force. By the time I was in kindergarten, he had left the military and settled into civilian life as a commercial pilot for Northwest Airlines, which merged with another carrier a few years ago. When Dad wasn't out on a trip, he and I would drive out to the Minneapolis–Saint Paul International Airport and park along the runway access road. I'd scramble up on the hood of our burgundy '65 Mustang, and we'd spend whole afternoons watching planes take off and land. Amid the roar of the engines and between blasts of jet fuel exhaust (the smell of which I loved, by the way), my dad would give me age-appropriate lessons in aerodynamics, air traffic control, and how to recognize types of airplanes by their fuselage and engine placement. When other kids declared that they wanted to be a fireman (usually boys) or a nurse (always girls) when they grew up, I would reply with similar conviction, and usually to a few teasing giggles, that I was going to be a pilot in the U.S. Air Force.

The author as an infant being held by her father, then an instructor pilot for the U.S. Air Force.

PHOTOS COURTESY OF WOODY FOUNTAIN

Aviator, glasses

Those career plans were crushed one brisk fall day when I was about seven years old. I was flying a kite with my dad at one of Minnesota's 10,000 lakes. We were under the glide path for planes landing at an airport nearby. A low, distant rumble announced a jet coming in on final approach. As it came into view, Dad quizzed me on the type of aircraft.

I recognized the distinct engine-in-the-tail profile.

"That's a 727," I chirped proudly.

"Yes, it's a United 727," he replied.

I squinted at the plane and turned to my dad. "How can you tell it's United?"

He furrowed his brow. "I can read it. Can't you?"

Tests would later confirm that I was not the victim of some blinding, degenerative disease. I was simply nearsighted. In the early 1970s, however, anyone with designs on a career in military aviation had to have 20/20 vision without glasses or contacts. "Aviator glasses," I realized, was a cruel misnomer, meant to describe an off-duty fashion accessory, not a refractive aid.

From that day on, I could be a fireman. I could even be a nurse. I could not, however, be a U.S. Air Force pilot.

Flight lessons

I got over this early disappointment (mostly) and discovered a rewarding career in medicine as an ophthalmologist. How's that for irony? Yet, I remain fascinated by aerodynamics. My dad has retired, but my mom will attest to the fact that he and I still talk about planes. A lot.

Over the years, I've come to recognize a number of parallels between medicine and aviation: They are both highly regulated institutions in which the barriers to entry are high. Both require long training periods. And, for both, the cost of failure is great.

In medicine, one of the greatest and costliest failures is misdiagnosis, defined as a failure to establish an accurate and timely explanation of the patient's health problem and communicate that explanation to the patient. A landmark 2015 report from the Institute of Medicine, now known as the National Academy of Medicine, estimated that twelve million people in the United States are misdiagnosed each year in the outpatient setting alone. This represents 5 percent of all patient encounters, making misdiagnosis a more common medical error than drug errors or wrong-site surgery.

In aviation, the greatest failure is the crash of an airliner. Fortunately, commercial failures are rare. When they do happen, I am

Woody Fountain, Tamara's father, stands next to a 747 he flew during his career as a pilot for Northwest Airlines (left). Tamara and her father, circa 1985, in a cockpit.

always anxious to call my dad and get his pilot's take on what might have gone wrong in the cockpit.

From our discussions, one crash in particular may have lessons for us in medicine.

Missed signals

Late at night on the last day of May 2009, Air France flight 447, a wide-body Airbus 330, took off from Rio de Janeiro headed for Paris. While cruising at 35,000 feet about three hours into flight, the airplane's speed indicator malfunctioned.

By itself, this malfunction would not cause the pilot to lose control of the craft. In fact, the airplane responded as it should: The autopilot disengaged because it was no longer receiving critical data on how fast the airplane was traveling. This instrument response is similar to what happens in a car if the speedometer malfunctions while cruise control is engaged. Cruise control cuts off, and the driver needs to take over.

The pilot in command, now forced to fly the plane manually, inexplicably executed a series of maneuvers that put the plane in a stall. Warnings and sirens blared as the plane began free fall in the nighttime sky.

The flight deck, according to the craft's flight recorder, or black box, was thrown into chaos. Checklists that should have been followed were not. Communication that should have taken place between the pilots did not. Direction, altitude, and other essential flight parameters that should have been monitored were not. The plane was falling toward the ocean at more than 10,000 feet per minute.

The most senior pilot, who had been on a rest break in the cabin when the speed indicator was lost, rushed back to the flight deck. Within seconds, he recognized the airplane was in an aerodynamic stall.

Recovery from a stall involves putting the plane into a dive to recover both airspeed and lift, then pulling out to level flight. It's a maneuver that should be instinctive for any pilot. Yet, by the time the crew made the right diagnosis, it was too late. They had run out of room. The last transmission from the flight deck was "F---, we're dead!"

A little more than 4 minutes after the autopilot disengaged, Air France 447 slammed belly-first into the Atlantic Ocean. All 228 aboard perished.

Signs and signifiers

My dad identifies what can be a common theme in airplane crashes—the pilots, he says, actually "forget to fly the airplane." A relatively minor distraction triggers a fatal cascade of events. The pilots lose situational awareness and, during the ensuing calamities, forget to ask three basic questions: Where am I? How fast am I going? In what direction am I headed?

Those three questions led me to think about how physicians fail to properly diagnose patients. The diagnoses we miss most often are common ailments, not exotic "zebras." In my field of ophthalmology, among the top diagnoses we miss are glaucoma, retinal detachment, and intraocular infection. A first-year resident would easily recognize all three. Yet, like the pilots of that ill-fated Air France flight, physicians who fail to connect the dots and recognize what should be obvious commit the medical equivalent of forgetting to fly the airplane. We physicians lose clinical situational awareness and, as a consequence, forget to treat the patient.

Time is in short supply during most patient encounters. Physicians must make quick triage and diagnostic assessments based on the constellation of signs and symptoms in front of them. This "fast," or intuitive, thinking, as described by psychologist Daniel Kahneman in his bestseller, *Thinking, Fast and Slow*, allows doctors to efficiently navigate through a forty-patient clinic day.

It is said that there are more than ten thousand diseases of the human body but only two hundred to three hundred symptoms. Diagnosing can be a challenge; it's understandable that our initial assessments are sometimes wrong. When they are, that's when what Kahneman describes as "slow," or deliberative, thinking should take over. When a patient doesn't respond to treatment as expected, the physician must step back and call a hard stop. To regain situational awareness, the following questions must be asked and answered: Why isn't this patient getting better? What do history, exam, and tests show? What else could this be?

Docs' black box

Aviation is the safest mode of travel in our country. More than nine million flights carry nearly one billion domestic passengers annually. There has not been a fatal crash of a U.S. commercial aircraft in nearly ten years. Because of the efforts of multiple federal agencies, including the Federal Aviation Administration and the National Transportation Safety Board, U.S. air travel benefits from a culture of safety, continuous improvement, and regular feedback to all stakeholders. Pilots, however, are no more immune to cognitive biases or human error than physicians are: Improved technology in aircraft design and air traffic control has largely removed the opportunity for pilot error to bring down a plane.

The day when technology saves physicians from themselves is not yet here—and may never come.

It's when we consider the issue of patient safety that the parallels between aviation and medicine begin to break down. There are fundamental differences between the two that help explain why the safety record for medicine lags that for aviation.

One difference is sheer numbers. There are infinitely more physician-patient encounters every year than there are flights. Although electronic medical records and clinical registries amass volumes of patient-care data, we still lack the medical equivalent of the black box and the investigative transparency that allow federal agencies to pinpoint the root cause of every plane crash and even every near miss. The culture of medicine largely discourages transparency or critical analysis of mistakes. Diagnostic errors often go undetected, and feedback that could improve the performance of individual physicians remains generally unavailable.

Where is the technology that could help minimize physician error as it has for pilot error? Test tracking, warning systems, and clinical prompts, in theory, should be some of the advantages conferred by electronic medical records. Yet, any health care professional with experience on an electronic platform recognizes how much more difficult and distracting that platform can make finding, filtering, and interpreting the clinical data needed for optimal decision making.

I like to think electronic medical records are in their nascent, floppy-disk phase. It's my hope that technology will one day succeed in making the computerized patient interface as intuitive and interoperable as the digital devices we all now hold in our hands. Only when this happens will we be able to reliably harness the power of artificial intelligence to support the diagnostic process and improve patient safety.

The day when technology saves physicians from themselves is not yet here—and may never come. I expect no machine will ever match the nuanced faculties a human physician brings to a patient encounter. As complex a system as a multimillion-dollar modern aircraft is, it is simple when compared to the complexity and individual variation of the human body and the myriad ways disease can afflict it.

This complexity makes our role as physicians that much more critical and challenging. One piece of good news is that common diseases present commonly and in (mostly) common ways. The clues to the correct diagnosis are often hiding in plain sight if we just take the time to look for them.

The other good news? Physicians usually have more time to connect the dots than pilots do. HM

Tamara Fountain, MD '88, an ophthalmic plastic and reconstructive surgeon, is a professor in the Department of Ophthalmology at Rush University Medical Center in Chicago and a principal in Ophthalmology Partners, Ltd., in Deerfield, Illinois.

Obituaries

1940s

1945

Giulio D'Angio, MD
September 14, 2018

Stuart H. Q. Quan, MD
July 4, 2018

1946

John G. Freymann, MD
August 13, 2018

1947

Arthur M. Dannenberg Jr., MD
June 15, 2018

Lloyd H. Smith Jr., MD
June 18, 2018

1948

R. Thomas Linger, MD
July 23, 2018

1950s

1950

Marvin L. Sachs, MD
January 29, 2018

Rayma Babbitt Sharber, MD
October 31, 2018

1952

Dan A. Martin, MD
August 14, 2018

John F. Radebaugh Jr., MD
July 3, 2018

Lee C. Watkins, MD
August 11, 2018

1955

Macellis K. Glass, MD
November 11, 2018

Richard C. Miller, MD
August 7, 2018

Quentin R. Stiles, MD
June 23, 2018

1956

Andrew D. Dorr, MD
November 11, 2018

1957

Daniel L. Gornel, MD
October 2018

Gustave C. Mueller, MD
November 12, 2018

1959

Ting K. Li, MD
November 18, 2018

Eli C. Messinger, MD
June 22, 2018

1960s

1960

Hans C. Rilling, PhD
October 16, 2018

1963

Richard F. Brubaker, MD
October 23, 2018

1966

Paul I. Winig, MD
September 9, 2018

1969

Michael W. Swanson, MD
October 24, 2018

1970s

1972

Steven G. Herbert, MD
November 20, 2018

1974

Bruce G. Wallace, PhD
July 13, 2018

1975

Nelson M. Braslow, MD
July 9, 2018

1979

Michael H. King, MD
September 2, 2018

1980s

1983

Michael W. Canning, MD
September 26, 2018

1990s

1994

Richard Y. Lin, MD
August 12, 2018

2000s

2002

Malia M. Jackson, MD
August 28, 2018

This listing of deceased alumni includes those alumni whose notices of death were received between August 1 and November 30, 2018.

PRESIDENT'S REPORT

New Members, **New Award**

THE ALUMNI COUNCIL RETURNED TO CAMPUS THIS FALL for its first meeting of the 2018-2019 academic year. We welcomed new members Joanna "Mimi" Choi, MD '09 (Los Angeles), Ted Kohler, MD '72 (Seattle), Allison McDonough, MD '97 (Newton, Massachusetts), and Alfred Sommer, MD '67 (Baltimore). We are thrilled with the regional representation that our new cohort brings to the table.

Ed Hundert, MD '84, dean for medical education, and Stephanie Hunt, director of financial aid, updated us on financial aid at the School. Roughly 80 percent of students receive financial aid, which remains need-based at HMS and across the University. The Council's focus is to support HMS in providing students with the financial support they need to not only attend HMS, but also to pursue their chosen careers after graduation.

Members were pleased to learn two key facts: HMS students carry 42 percent less debt than their peers who graduate from other private medical schools, and HMS provides full tuition and fees for students with full need.

Last spring, the Council helped develop an alumni survey to support the Liaison Committee on Medical Education reaccreditation self-study phase. We had an astounding 27 percent participation rate, which included graduates in forty-six states. Ninety-six percent of us report being satisfied with our HMS education, and 94 percent said they would choose to attend HMS again. Results are still being assessed by generation, specialty, and region and to identify trends and actionable items. Thank you again to all who participated.

Dean George Daley, MD '91, discussed with us his developing strategic plan. The plan applies cross-cutting goals to mission-level priorities, including teaching and learning; scholarship and discovery; and service and leadership. On behalf of alumni, the Council shared thoughts on a draft of the School's new mission statement, which highlights what HMS stands for as a school, as a research institution, and as an organization committed to improving human health.

Finally, we began discussions on a program we're developing—the Distinguished Service Award for Harvard Medical School Alumni. The award, the first alumni-specific one at the School, will recognize and celebrate alumni who demonstrate loyalty, service, and commitment to HMS through volunteering, community building, service as an ambassador for the School, or otherwise supporting HMS and its mission. The Alumni Council will serve as the selection committee this year. Nomination inquiries can be sent to **hmsalum@hms.harvard.edu**. We look forward to announcing the first recipient of this award at our annual business meeting during Alumni Day and Reunion on Friday, June 7, 2019.

Thank you to all alumni for your support of our mission and our students!

Elizabeth (Lisa) Petri Henske, MD '85, is an HMS professor of medicine at Brigham and Women's Hospital, director of the Center for LAM Research and Clinical Care at Brigham and Women's, director of the Brigham Research Institute, associate member of the Broad Institute of MIT and Harvard, and a medical oncologist at the Lank Center for Genitourinary Oncology at Dana-Farber Cancer Institute.

Alumni Announcements

Harvard Alumni Directory

Interested in finding and networking with fellow Harvard alumni? Look no further than the Harvard Alumni Directory. As a graduate of HMS, you are a member of the Harvard Alumni Association and eligible for benefits such as the Harvard Alumni Directory. Use your HarvardKey log in to access the online directory at **alumni.harvard.edu/community** and search for alumni by industry, region, specialty, class year, and more.

Alumni Day 2019

Mark your calendar for June 7, 2019, and attend Alumni Day, a day for alumni to reconnect with fellow MD grads. Program highlights include the dean's State of the School address, the Harvard Medical Alumni Association's annual meeting, the Alumni Day Symposium, and campus tours. Members of the Society of the Silver Stethoscope—alumni who have celebrated their 60th reunion—are invited to a private lunch. Visit **alumni.hms.harvard.edu/alumni-day** for details.

Discount on online continuing medical education courses

Enjoy a 25 percent discount on self-paced, online courses taught by the School's renowned faculty. HMS Global Academy has both accredited and nonaccredited content available for medical professionals. To access these courses, go to **globalacademy.hms.harvard.edu**, create your own CME account, and use the code Alumni25 to enroll.

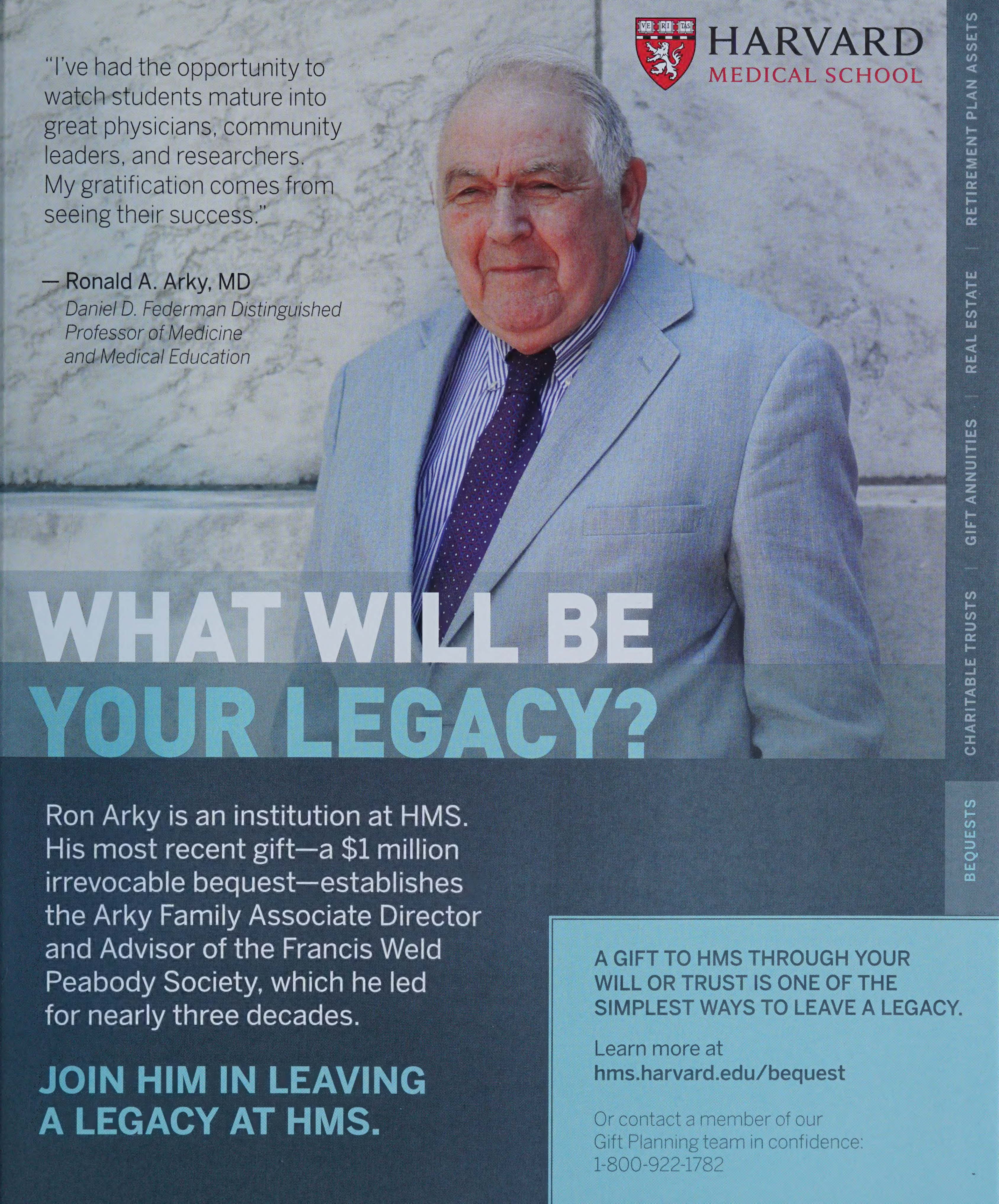
How can we reach you?

Stay informed on all the latest HMS news, exclusive alumni benefits, reunion notices, and networking and professional events. We send communications most often by email, so be sure to update your information at **alumni.hms.harvard.edu/email-update**.

Share your memories and insights

How does being a physician bring you joy? What are your thoughts on burnout? These are two questions being posed for "Rounds," a special section of *Harvard Medicine* magazine for alumni voices. Visit **alumni.hms.harvard.edu/rounds** to share your thoughts and opinions. Responses will be featured in future issues of the magazine.

RANDY GLASS


HARVARD
MEDICAL SCHOOL
VE RI TAS
"I've had the opportunity to watch students mature into great physicians, community leaders, and researchers. My gratification comes from seeing their success."
— Ronald A. Arky, MD
Daniel D. Federman Distinguished Professor of Medicine and Medical Education
WHAT WILL BE
YOUR LEGACY?
BEQUESTS | CHARITABLE TRUSTS | GIFT ANNUITIES | REAL ESTATE | RETIREMENT PLAN ASSETS
Ron Arky is an institution at HMS. His most recent gift—a $1 million irrevocable bequest—establishes the Arky Family Associate Director and Advisor of the Francis Weld Peabody Society, which he led for nearly three decades.
JOIN HIM IN LEAVING A LEGACY AT HMS.
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1-800-922-1782

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MEDICAL SCHOOL

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By the Numbers

The computational tools being used to analyze medical data for patterns that can inform diagnosis, therapeutic choices, and long-term care draw upon vast stores of numbers, values, and other measures gathered from patients.